STEROIDAL REARRANGEMENTS

RESUME

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

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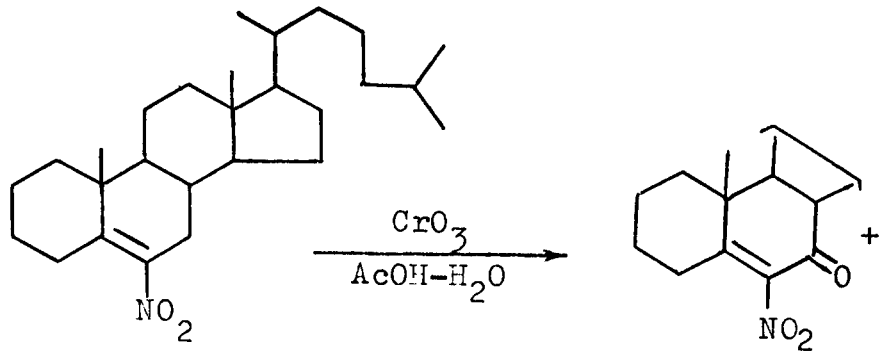
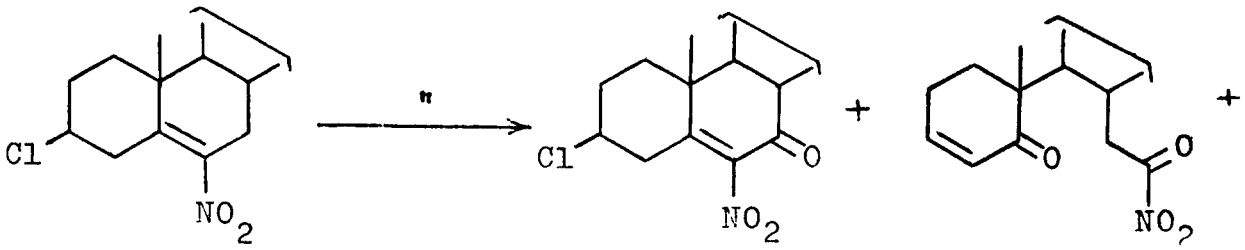
PART - ONE

Oxidation of Steroidal Nitro Olefins

Chromium (VI) oxidation of carbon carbon double bond can lead to the formation of a large variety of compounds such as α-glycols, α-ketals and cleavage products. In addition oxidation of allylic carbon-hydrogen bonds is also observed. Oxidation of steroidal compounds having carbon-carbon double bond has been studied in great deal, but carbon-carbon double bond oxidation attached with an electron withdrawing group e.g. nitro olefin, which finds unique place in synthetic steroidal methodology, remained unexplored so far. We, therefore, undertook oxidation of easily accessible steroidal nitro olefins such as 6-nitrocholest-5-ene (I), 3β-chloro-6-nitrocholest-5-ene (II) and 3β-acetoxy-6-nitrocholest-5-ene (III). The products obtained, by allylic oxidation and ring cleavage, were identified on the basis of their spectral properties and the mechanism of oxidation has been shown in scheme-1.



(I) (IV) (V)



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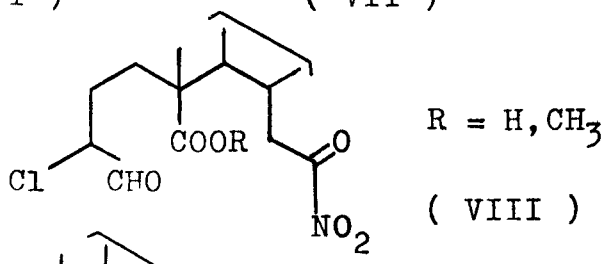
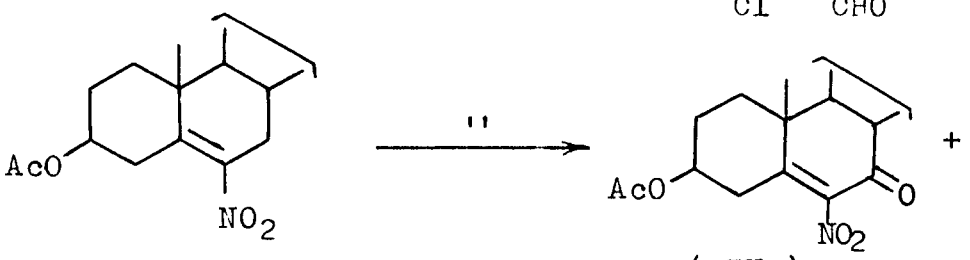
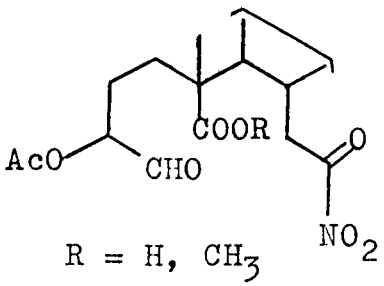


R = H, CH_3

(VIII)



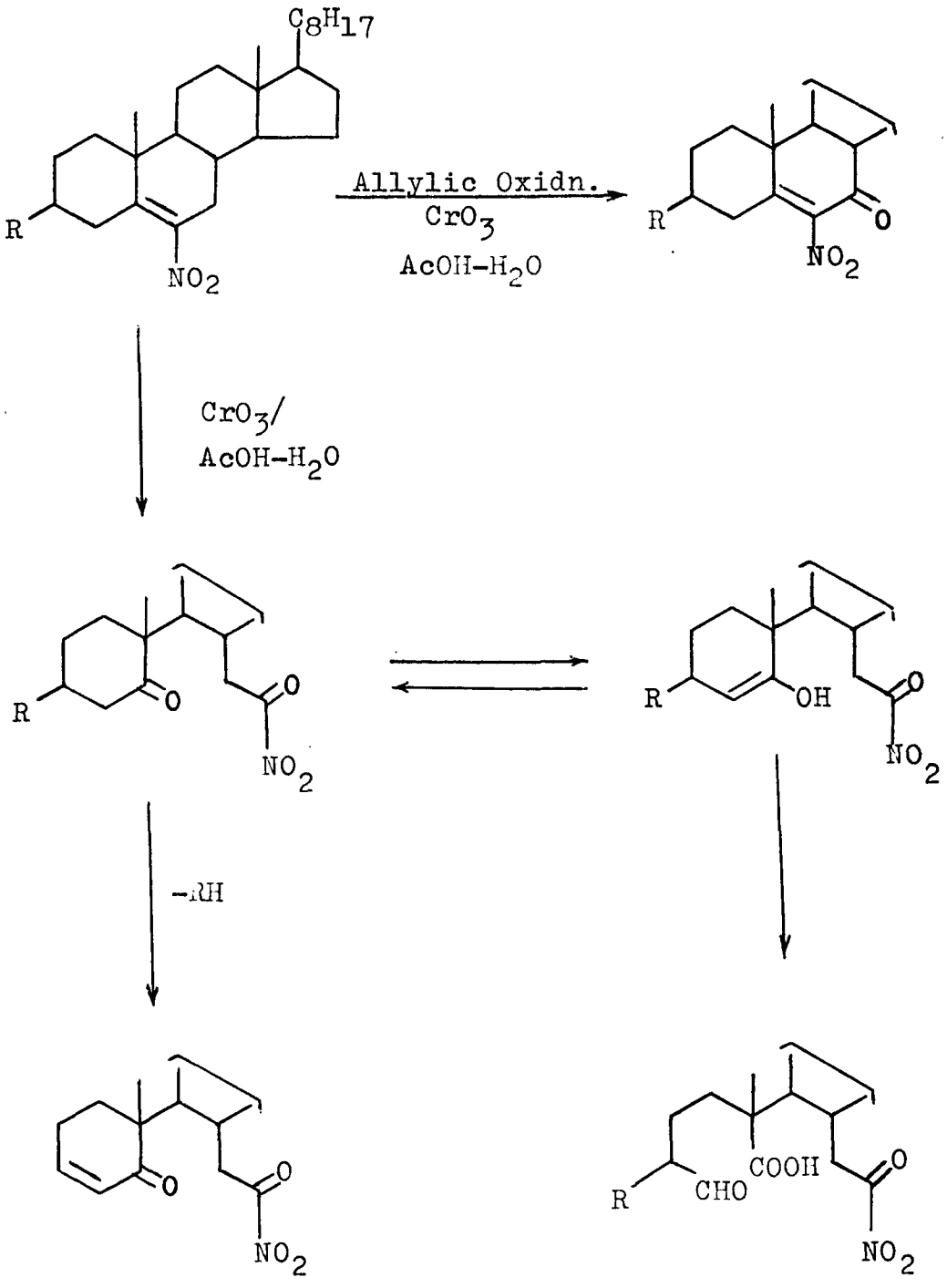
(III) (IX)



R = H, CH_3

(X)

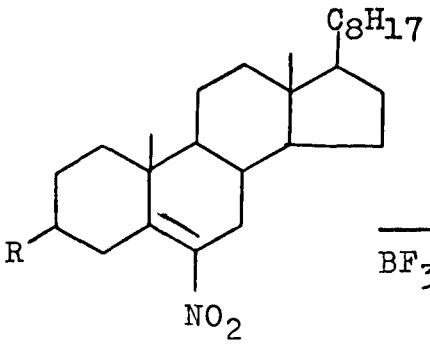
Scheme - 1


C_8H_{17}
R
NO_2
Allylic Oxidn.
CrO_3
$AcOH-H_2O$
O
CrO_3/
$AcOH-H_2O$
OH
-RH
COOH
CHO

PART - TWO

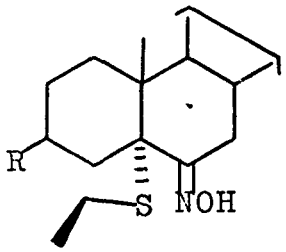
Reduction of Steroidal Nitro Olefins

Asymmetric addition of thiols to α,β-unsaturated compounds is a reaction that possesses a potential applicability to the synthesis of physiologically active substances having a chiral centre at the α- or β- position of the sulphur atom and a topic of current interest. A survey of literature revealed that nitro olefins undergo Michael addition reaction on treatment with thiols, resulting in the formation of nitro thioethers. In some cases, the nitro olefins undergo Michael addition followed by the cleavage of carbon carbon double bond with subsequent attack of another molecule of the thiol to give dithioethers. Prompted by these observations, we carried out similar reactions of steroidal nitro olefins (I, II, III) with thiols and contrary to our expectations, the compounds obtained were those which underwent nitro to oximino group rearrangement after Michael addition of thiol at the α- carbon and have no precedence in the literature. The compounds (XI-XIII) and (XIV-XVI) were acetylated with acetic anhydride and pyridine to give acetyl derivatives(XX-XXV). The products were characterized on the basis of their spectral and chemical properties and the mechanism of the reduction has been given (scheme-2).



CH_3CH_2SH

$BF_3:Et_2O, CH_2Cl_2$

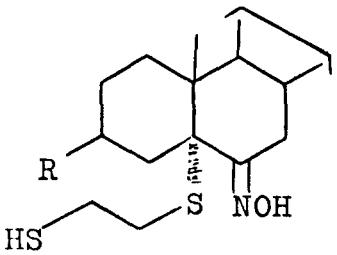


	R
(I)	H
(II)	Cl
(III)	OAc

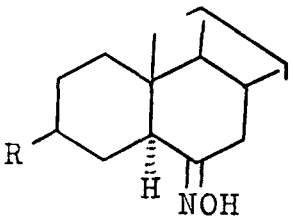
	R
(XI)	H
(XII)	Cl
(XIII)	OAc

SH, SH, — $BF_3:Et_2O$, CH_2Cl_2

Raney Ni, EtOH/Reflux

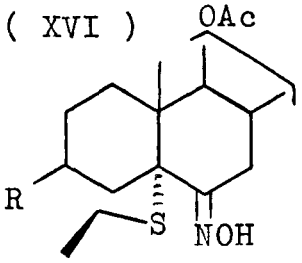


Raney-Ni, EtOH/Reflux

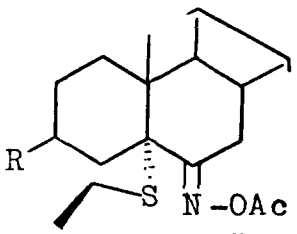


	R
(XIV)	H
(XV)	Cl
(XVI)	OAc

	R
(XVII)	H
(XVIII)	Cl
(XIX)	OAc

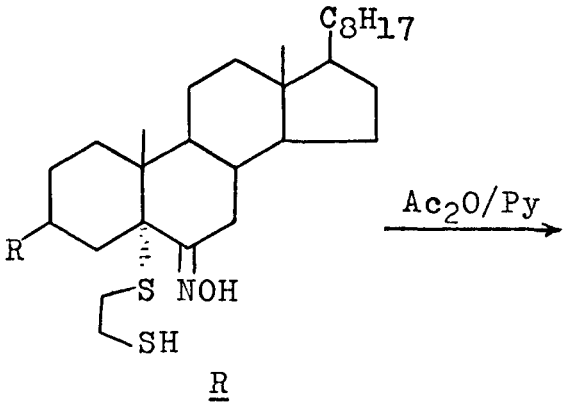


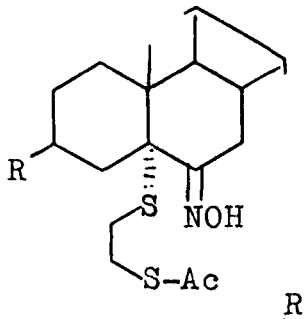
Ac_2O/Py



	R
(XI)	H
(XII)	Cl
(XIII)	OAc

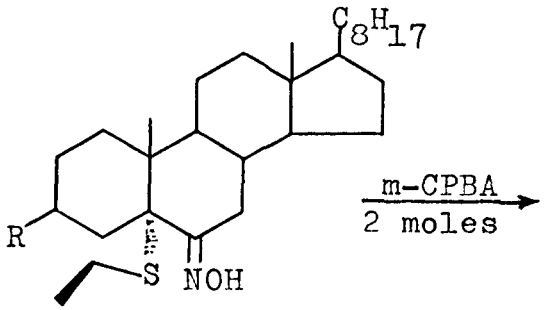
	R
(XX)	H
(XXI)	Cl
(XXII)	OAc

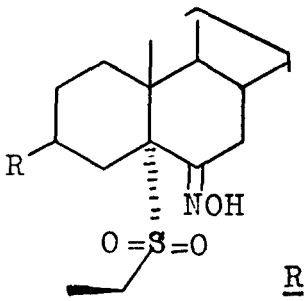




	R		R
(XIV)	H	(XXIII)	H
(XV)	Cl	(XXIV)	Cl
(XVI)	OAc	(XXV)	OAc

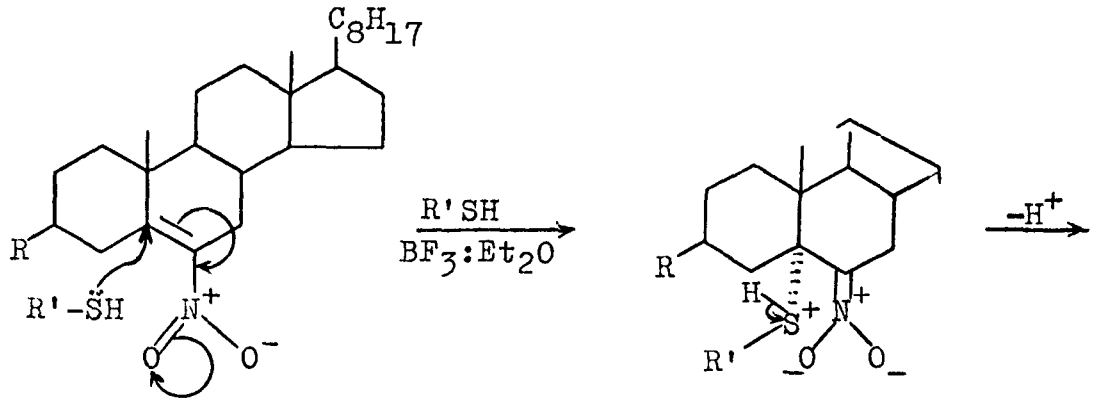
The sulphone derivatives of (XII) and (XIII) were prepared by treating these compounds with m-chloroperbenzoic acid. The compounds XXVI and XXVII, thus obtained were identified on the basis of their spectral properties.



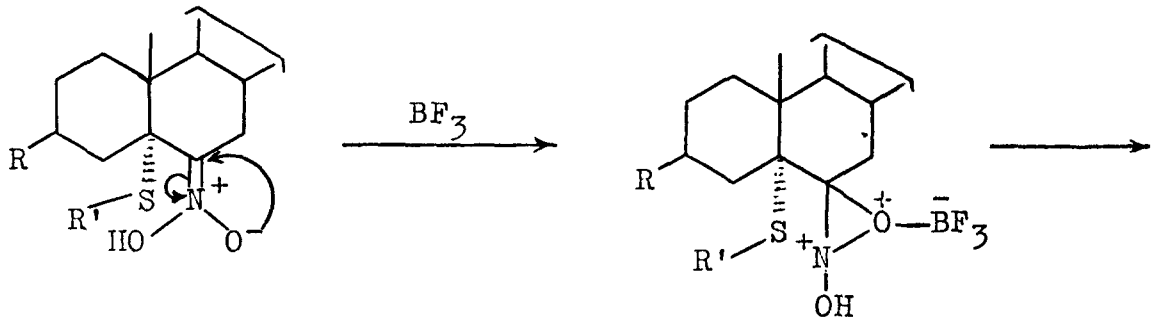


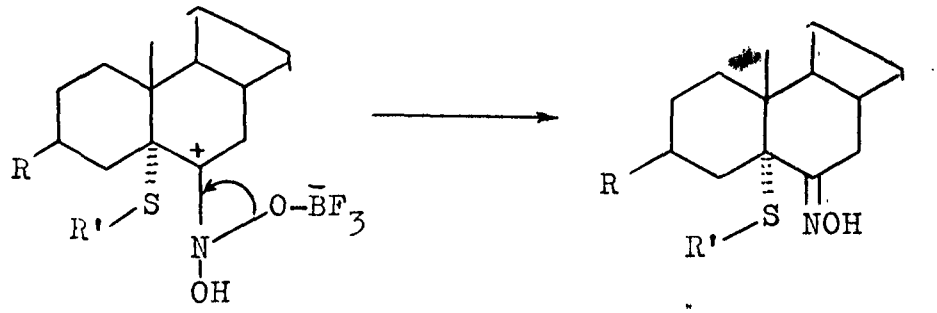
	R		R
(XII)	Cl	(XXVI)	Cl
(XIII)	OAc	(XXVII)	OAc

Scheme - 2



R = H, Cl, OAc





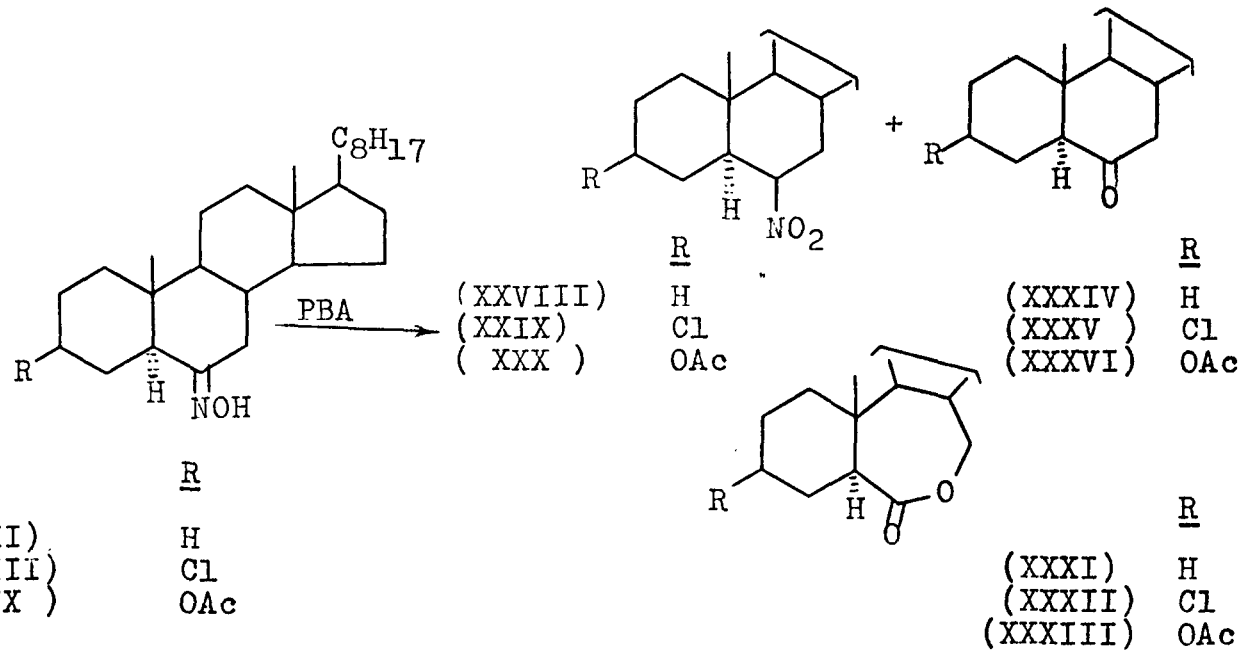
R' = CH_3-CH_2-

= $HS(CH_2)_2$ -

PART - THREE

Oxidation of Steroidal Oximes

The carbonyl and nitro functional groups play a major role in organic synthesis. The efficient conversion of one to the other, which enhances its utility, is readily accomplished in nitro to carbonyl direction. However, the conversion of carbonyl to nitro group, which is generally effected via oximes using very strong and non selective oxidants, is at present only narrowly applicable. We have made an attempt to explore the possibility of converting steroidal ketoximes to nitro compounds with the help of perbenzoic acid and obtained nitro compounds along with deoximated ketones which also gave lactones due to Bayer-Villiger oxidation with perbenzoic acid.



	R
(XVII)	H
(XVIII)	Cl
(XIX)	OAc

	R
(XXVIII)	H
(XXIX)	Cl
(XXX)	OAc

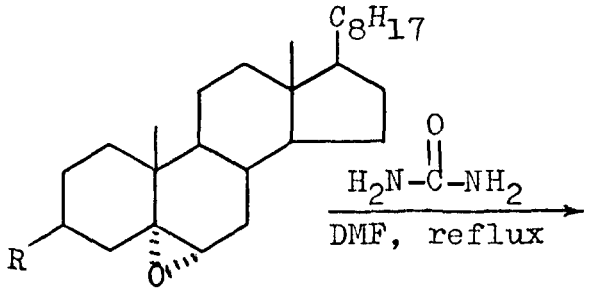
	R
(XXXIV)	H
(XXXV)	Cl
(XXXVI)	OAc

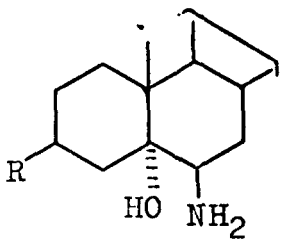
	R
(XXXI)	H
(XXXII)	Cl
(XXXIII)	OAc

PART - FOUR

Preparation of Aminosterols

Synthesis of steroidal vicinal amino alcohols has drawn the attention of chemists for the last so many years due to their non-hormonal biological activities. A number of synthetic routes have been adopted by different workers. Most commonly,oxirane ring is opened by sodium azide to give azido alcohol which on reduction with lithium aluminium hydride gave aminosterol. We have prepared aminosterols by opening epoxide ring with urea which gave various amino alcohols. The products were identified on the basis of their spectral properties.

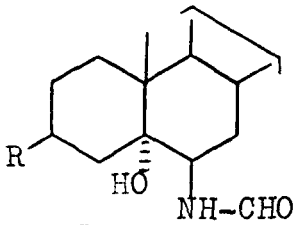




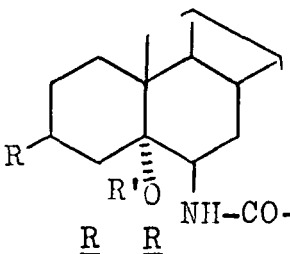
+

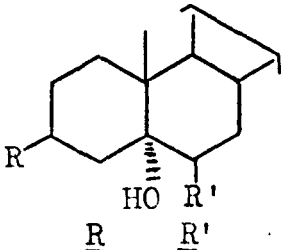
	R
(XXXVII)	H
(XXXVIII)	Cl
(XXXIX)	OAc

	R
(XL)	H
(XLI)	Cl
(XLII)	OAc



+





	R
(XLIII)	H
(XLIV)	Cl
(XLV)	OAc

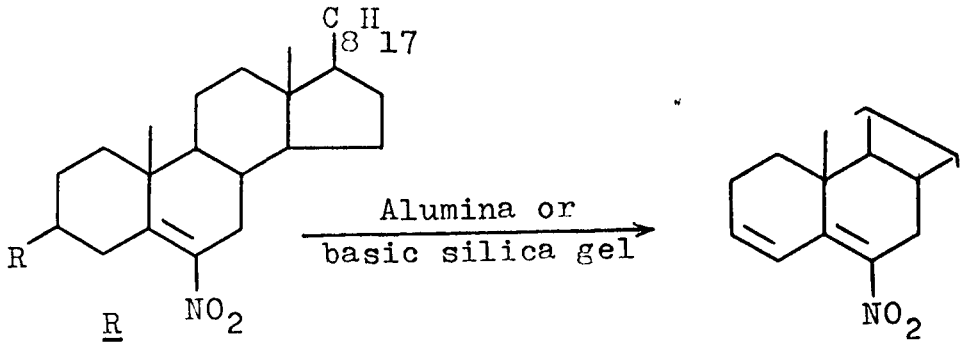
	R	R
(XLVI)	H	H
(XLVII)	Cl	H
(XLVIII)	OAc	H
(LII)	OAc	Ac

	R	R'
(XLIX)	H	OH
(L)	Cl	OH
(LI)	OAc	OH
(LIa)	OAc	NHCOOH

PART - FIVE

Steroidal Transformations on Solid Surface

Alumina as a catalyst or as catalyst support finds multiple uses in general processes like dehydration, isomerization. Similarly, silica gel is an effective reagent for rapid dehydration of allylic, tertiary and sterically hindered secondary alcohols at room temperature. We have utilized the above given properties of alumina and silica gel for the preparation of conjugated cyclic nitro olefin and $\alpha,\beta,\gamma,\delta$-unsaturated ketone. The products were identified on the basis of their chemical and spectral properties. The mechanism of the alumina/silica gel induced transformation has been given (scheme 3a, b).

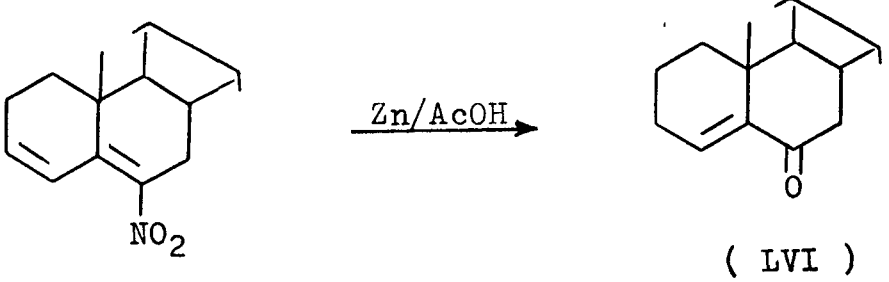


R

(III) OAc

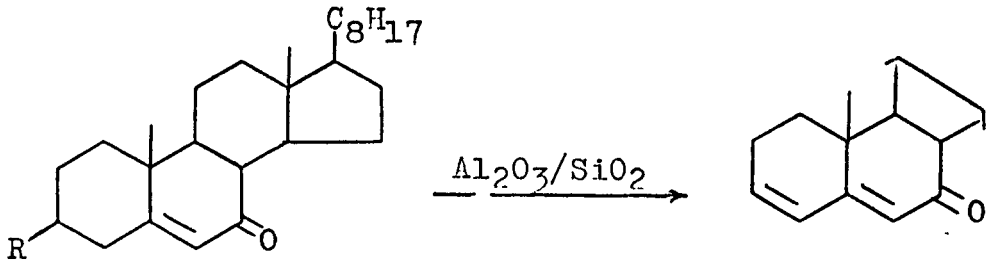
(LIII) OH

(LIV)



(LV)

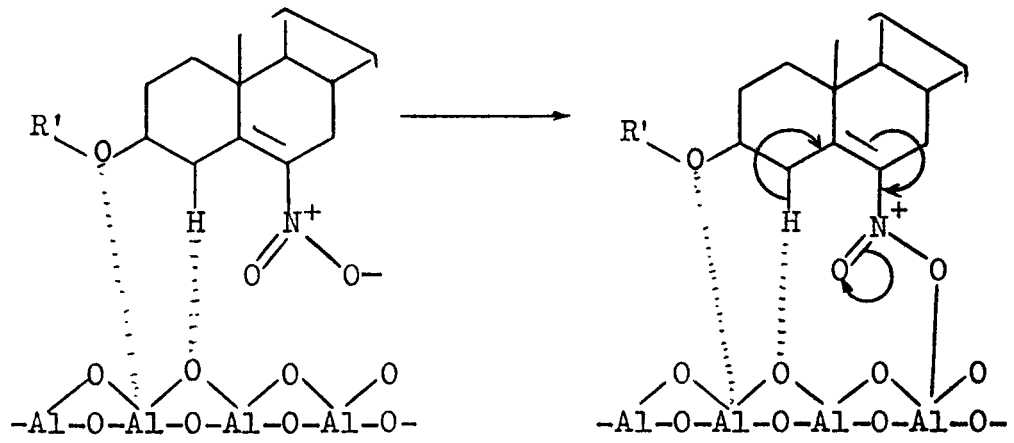
(LVI)



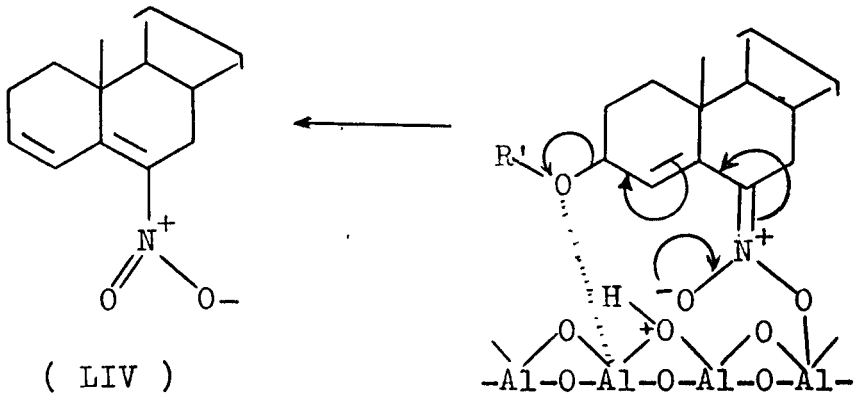
	R
(LVII)	OH
(LVIII)	OAc

(LIX)

Scheme - 3a

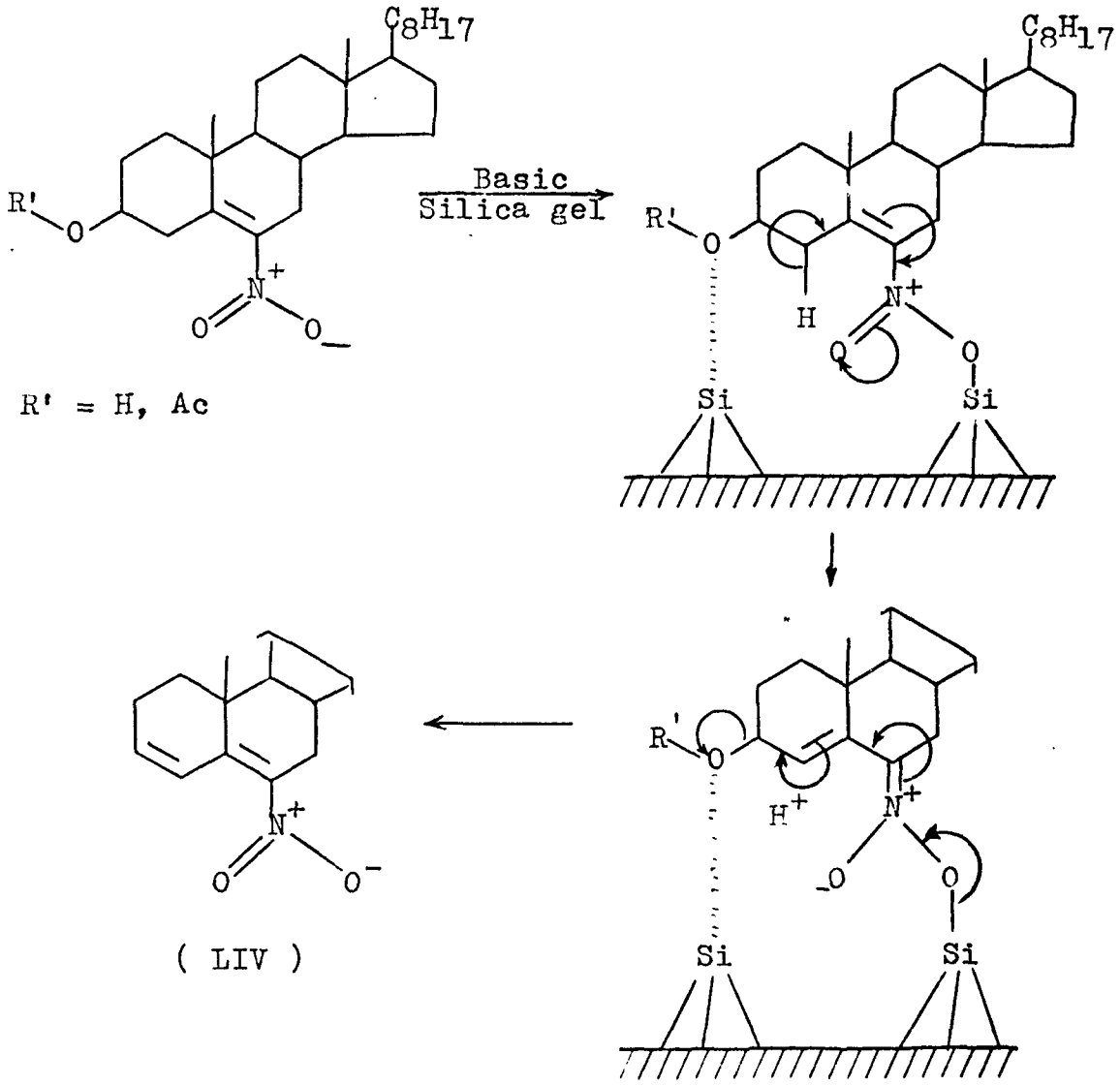


R' = H, Ac



(LIV)

Scheme - 3b



R' = H, Ac

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1984

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Dr. Shafiullah

Reader,
Steroid Research Laboratory
Department of Chemistry

Date: 26.7.1984

This is to certify that the work embodied in this thesis entitled, "Steroidal Rearrangements", is the original work of Mr. Raj Kumar Singh carried out under my supervision. The thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

Shafiullah

(SHAFIULLAH)

ACKNOWLEDGEMENTS

I express my deepest sence of gratitude to Dr. Shafiullah for his able guidance and supervision throughout this research work and to Professor M.S. Ahmad, Chairman, Department of Chemistry, A.M.U. Aligarh, for his generous help and discussions, which made this work take its present shape. He was a constant source of inspiration and encouragement for me. I am thankful to Professor W. Rahman, former chairman, Department of Chemistry for providing necessary facilities and to Professor H. Ogura and H. Takayanagi, Kitasato University, Japan for spectral analysis.

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(RAJ KUMAR SINGH)

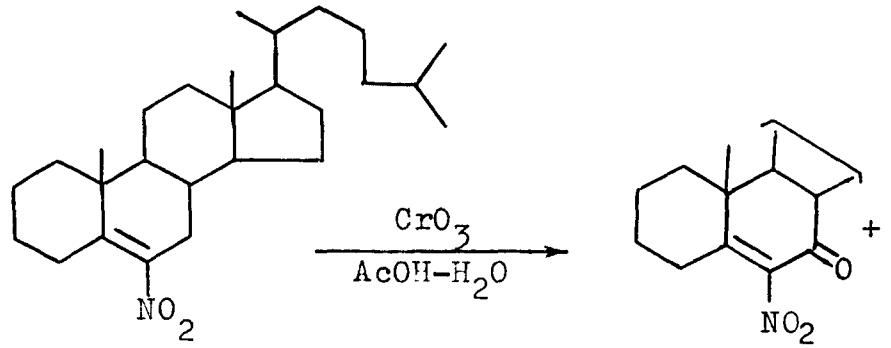
C O N T E N T S

SUMMARY

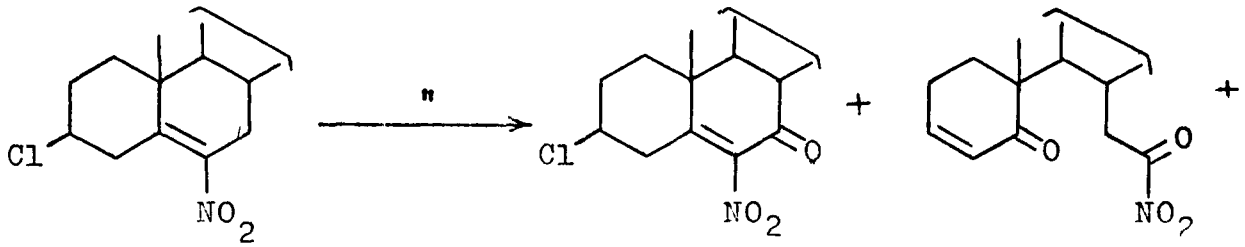
PART - ONE

Oxidation of Steroidal Nitro Olefins

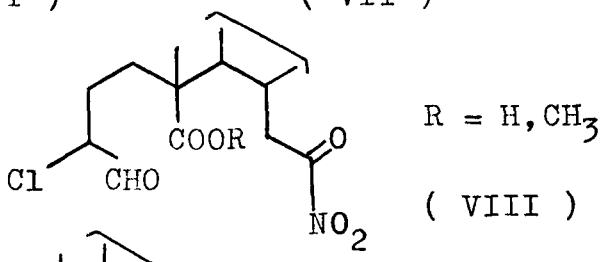
Chromium (VI) oxidation of carbon carbon double bond can lead to the formation of a large variety of compounds such as α-glycols, α-ketals and cleavage products. In addition oxidation of allylic carbon-hydrogen bonds is also observed. Oxidation of steroidal compounds having carbon-carbon double bond has been studied in great deal, but carbon-carbon double bond oxidation attached with an electron withdrawing group e.g. nitro olefin, which finds unique place in synthetic steroidal methodology, remained unexplored so far. We, therefore, undertook oxidation of easily accessible steroidal nitro olefins such as 6-nitrocholest-5-ene (I), 3β-chloro-6-nitrocholest-5-ene (II) and 3β-acetoxy-6-nitrocholest-5-ene (III). The products obtained, by allylic oxidation and ring cleavage, were identified on the basis of their spectral properties and the mechanism of oxidation has been shown in scheme-1.



(I) (IV) (V)

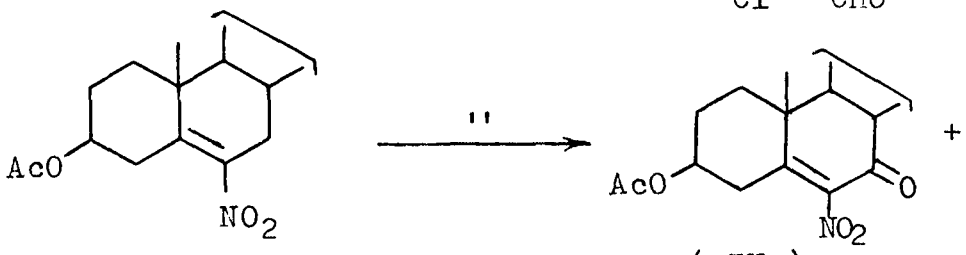


(II) (VI) (VII)



R = H, CH_3

(VIII)



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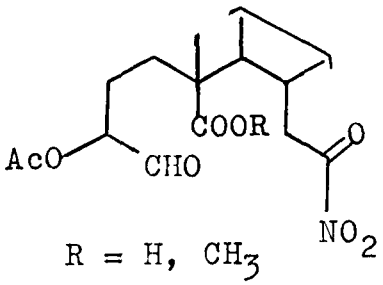
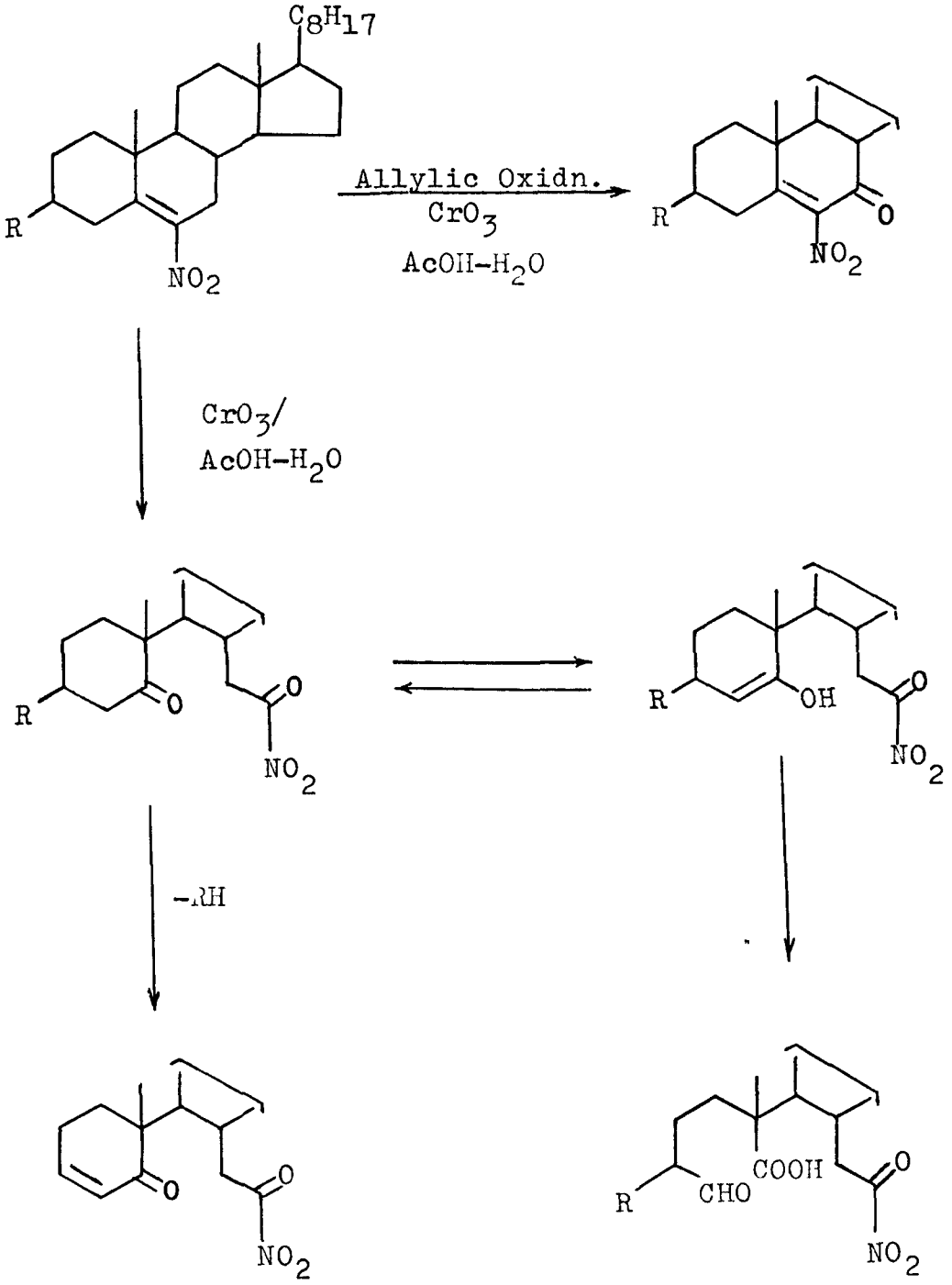


R = H, CH_3

(X)

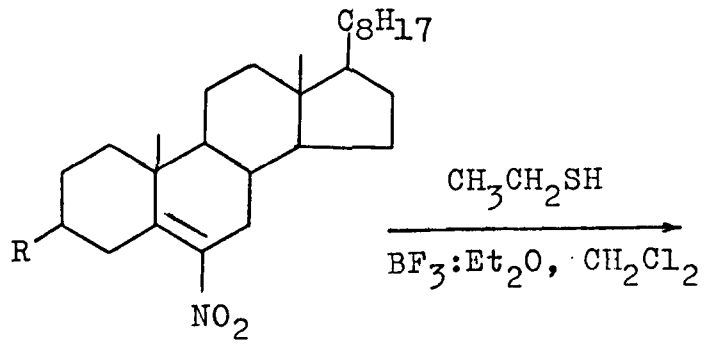
Scheme - 1


C_8H_{17}
R
NO_2
Allylic Oxidn.
CrO_3
$AcOH-H_2O$
R
O
NO_2
CrO_3/
$AcOH-H_2O$
R
O
O
NO_2
R
OH
O
NO_2
-RH
O
O
NO_2
R
CHO
COOH
O
NO_2

PART - TWO

Reduction of Steroidal Nitro Olefins

Asymmetric addition of thiols to α,β-unsaturated compounds is a reaction that possesses a potential applicability to the synthesis of physiologically active substances having a chiral centre at the α- or β- position of the sulphur atom and a topic of current interest. A survey of literature revealed that nitro olefins undergo Michael addition reaction on treatment with thiols, resulting in the formation of nitro thioethers. In some cases, the nitro olefins undergo Michael addition followed by the cleavage of carbon carbon double bond with subsequent attack of another molecule of the thiol to give dithioethers. Prompted by these observations, we carried out similar reactions of steroidal nitro olefins (I, II, III) with thiols and contrary to our expectations, the compounds obtained were those which underwent nitro to oximino group rearrangement after Michael addition of thiol at the α- carbon and have no precedence in the literature. The compounds (XI-XIII) and (XIV-XVI) were acetylated with acetic anhydride and pyridine to give acetyl derivatives(XX-XXV). The products were characterized on the basis of their spectral and chemical properties and the mechanism of the reduction has been given (scheme-2).

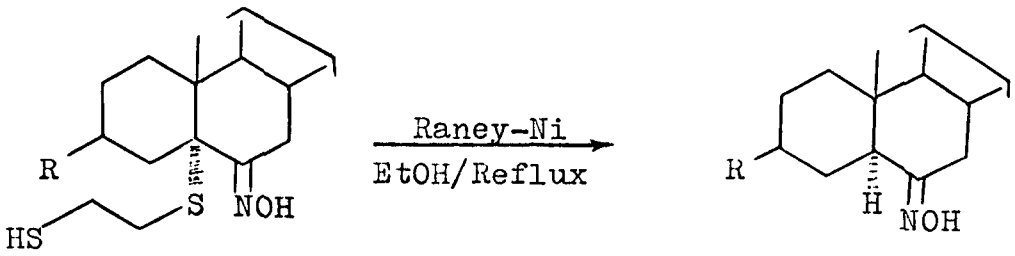


	R
(I)	H
(II)	Cl
(III)	OAc

	R
(XI)	H
(XII)	Cl
(XIII)	OAc

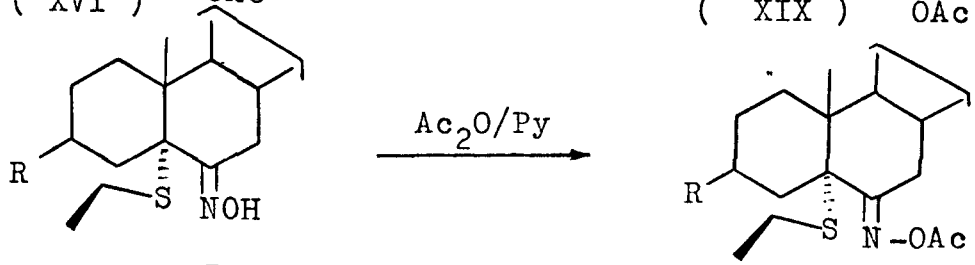
SH
SH, $BF_3:Et_2O$, CH_2Cl_2

Raney Ni
EtOH/Reflux



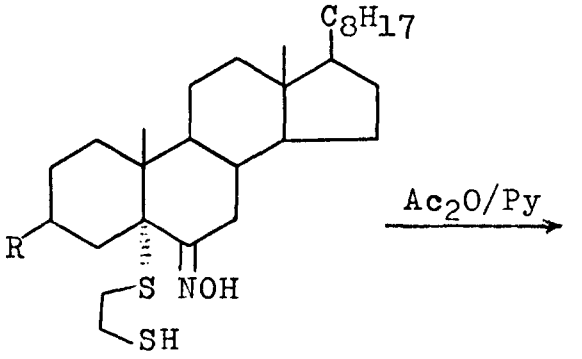
	R
(XIV)	H
(XV)	Cl
(XVI)	OAc

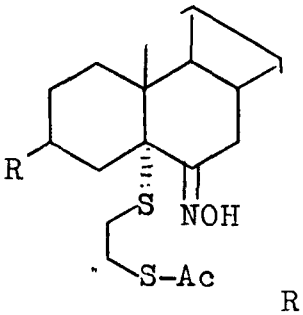
	R
(XVII)	H
(XVIII)	Cl
(XIX)	OAc



	R
(XI)	H
(XII)	Cl
(XIII)	OAc

	R
(XX)	H
(XXI)	Cl
(XXII)	OAc

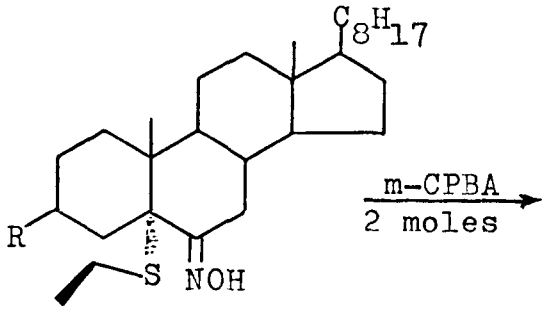


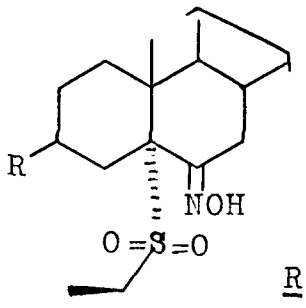


	R
(XIV)	H
(XV)	Cl
(XVI)	OAc

	R
(XXIII)	H
(XXIV)	Cl
(XXV)	OAc

The sulphone derivatives of (XII) and (XIII) were prepared by treating these compounds with m-chloroperbenzoic acid. The compounds XXVI and XXVII, thus obtained were identified on the basis of their spectral properties.

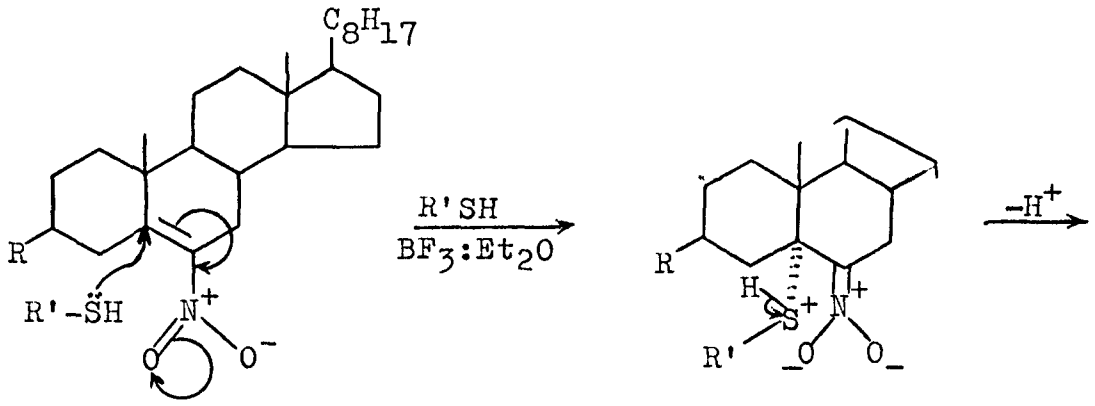




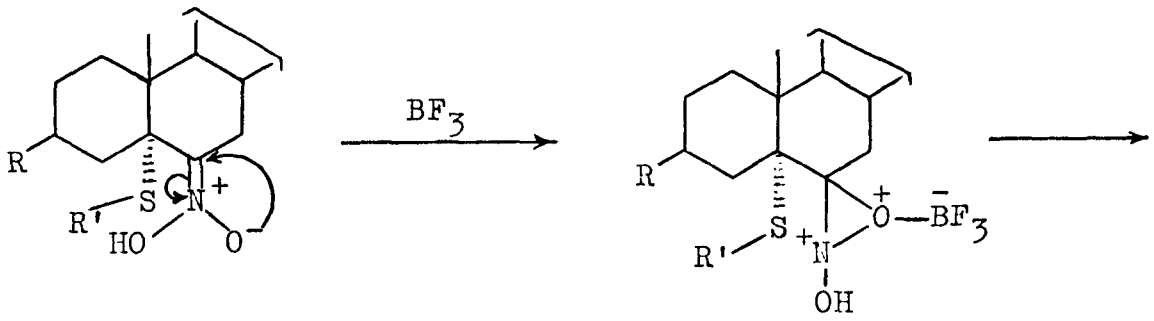
	R
(XII)	Cl
(XIII)	OAc

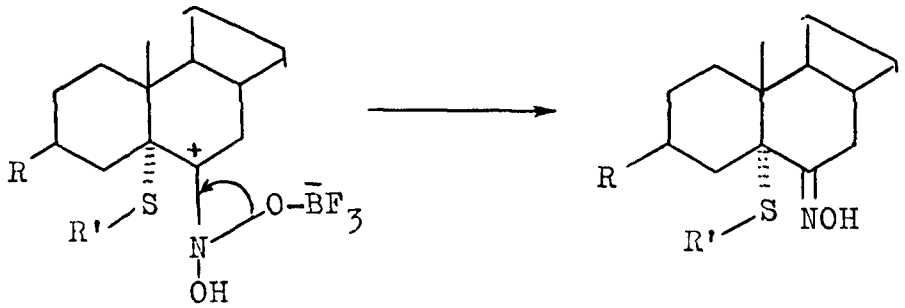
	R
(XXVI)	Cl
(XXVII)	OAc

Scheme - 2



R = H, Cl, OAc





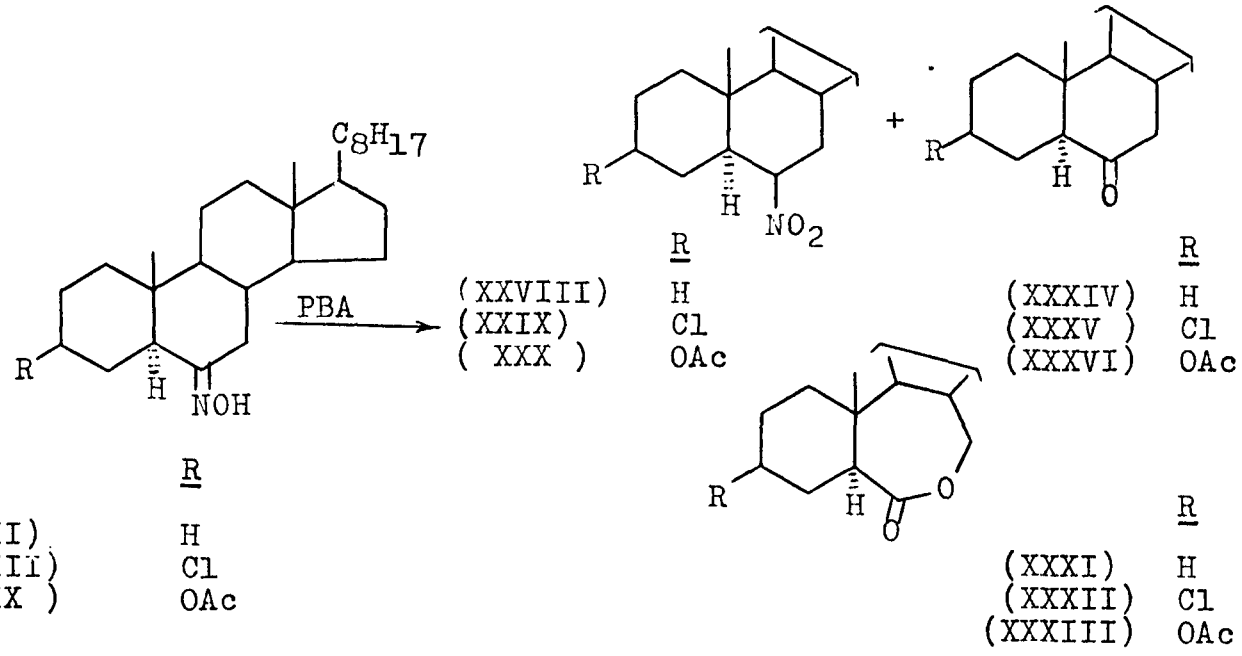
R' = CH_3-CH_2-

= $HS(CH_2)_2$ -

PART - THREE

Oxidation of Steroidal Oximes

The carbonyl and nitro functional groups play a major role in organic synthesis. The efficient conversion of one to the other, which enhances its utility, is readily accomplished in nitro to carbonyl direction. However, the conversion of carbonyl to nitro group, which is generally effected via oximes using very strong and non selective oxidants, is at present only narrowly applicable. We have made an attempt to explore the possibility of converting steroidal ketoximes to nitro compounds with the help of perbenzoic acid and obtained nitro compounds along with deoximated ketones which also gave lactones due to Bayer-Villiger oxidation with perbenzoic acid.



	R
(XVII)	H
(XVIII)	Cl
(XIX)	OAc

	R
(XXVIII)	H
(XXIX)	Cl
(XXX)	OAc

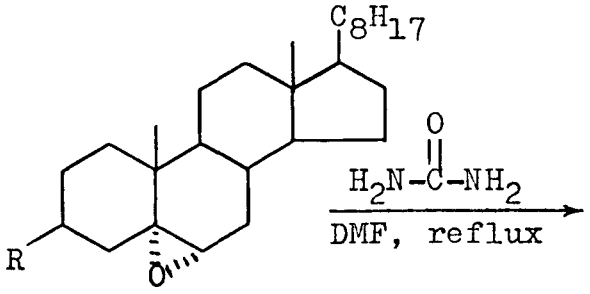
	R
(XXXIV)	H
(XXXV)	Cl
(XXXVI)	OAc

	R
(XXXI)	H
(XXXII)	Cl
(XXXIII)	OAc

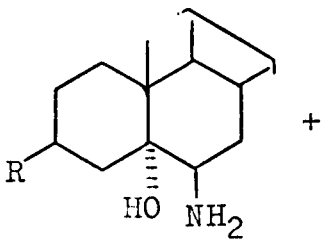
PART - FOUR

Preparation of Aminosterols

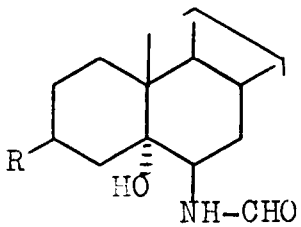
Synthesis of steroidal vicinal amino alcohols has drawn the attention of chemists for the last so many years due to their non-hormonal biological activities. A number of synthetic routes have been adopted by different workers. Most commonly, oxirane ring is opened by sodium azide to give azido alcohol which on reduction with lithium aluminium hydride gave aminosterol. We have prepared aminosterols by opening epoxide ring with urea which gave various amino alcohols. The products were identified on the basis of their spectral properties.



	R
(XXXVII)	H
(XXXVIII)	Cl
(XXXIX)	OAc

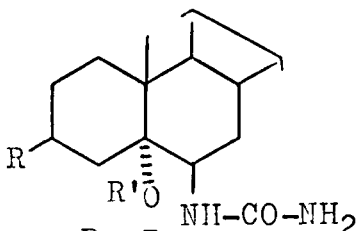


	R
(XL)	H
(XLI)	Cl
(XLII)	OAc

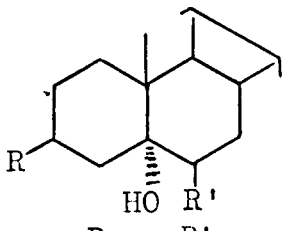


	R
(XLIII)	H
(XLIV)	Cl
(XLV)	OAc

+



	R	R
(XLVI)	H	H
(XLVII)	Cl	H
(XLVIII)	OAc	H
(LII)	OAc	Ac

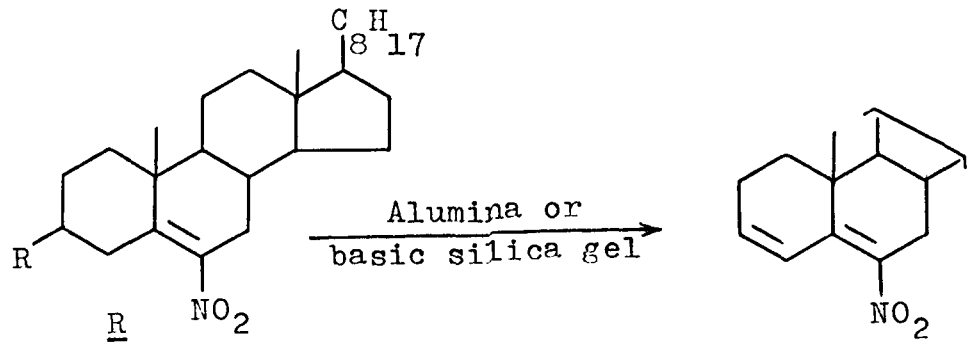


	R	R'
(XLIX)	H	OH
(L)	Cl	OH
(LI)	OAc	OH
(LIa)	OAc	NHCOOH

PART - FIVE

Steroidal Transformations on Solid Surface

Alumina as a catalyst or as catalyst support finds multiple uses in general processes like dehydration, isomerization. Similarly, silica gel is an effective reagent for rapid dehydration of allylic, tertiary and sterically hindered secondary alcohols at room temperature. We have utilized the above given properties of alumina and silica gel for the preparation of conjugated cyclic nitro olefin and α,β,γ,δ-unsaturated ketone. The products were identified on the basis of their chemical and spectral properties. The mechanism of the alumina/silica gel induced transformation has been given (scheme 3a, b).

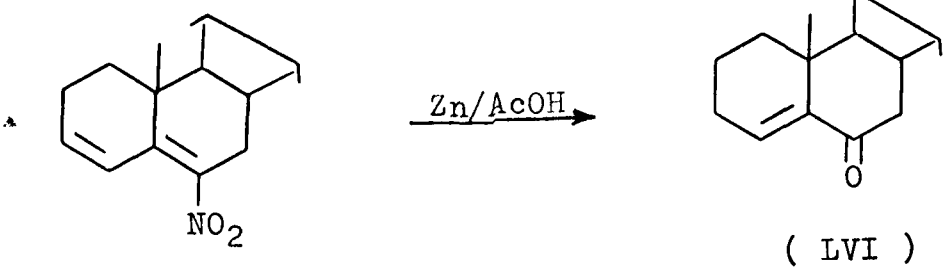


R

(III) OAc

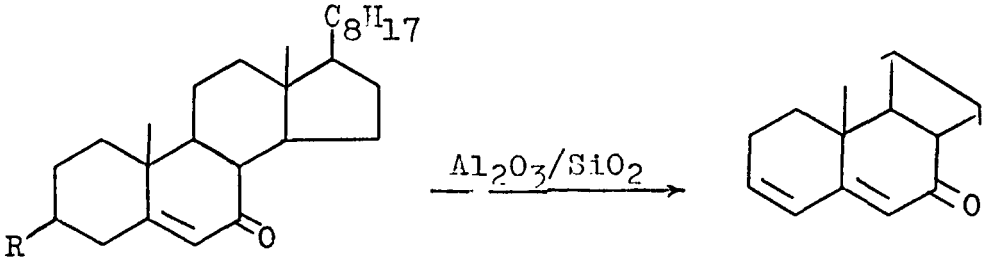
(LIII) OH

(LIV)



(LV)

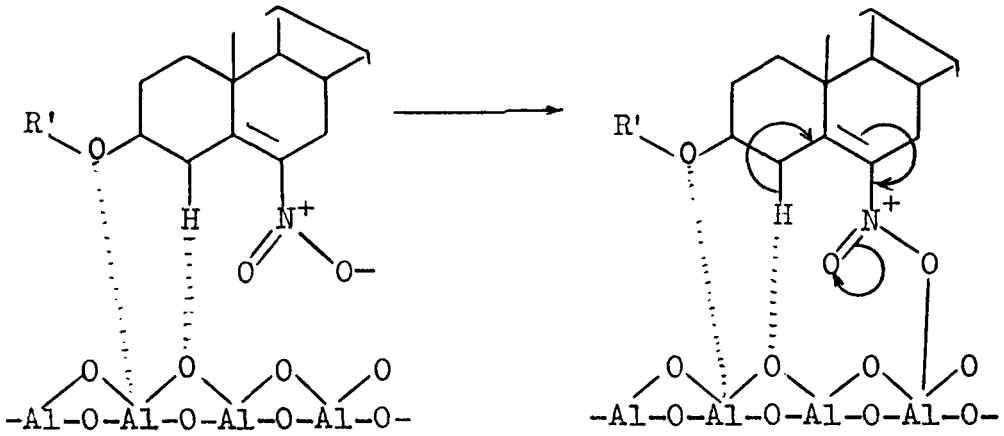
(LVI)



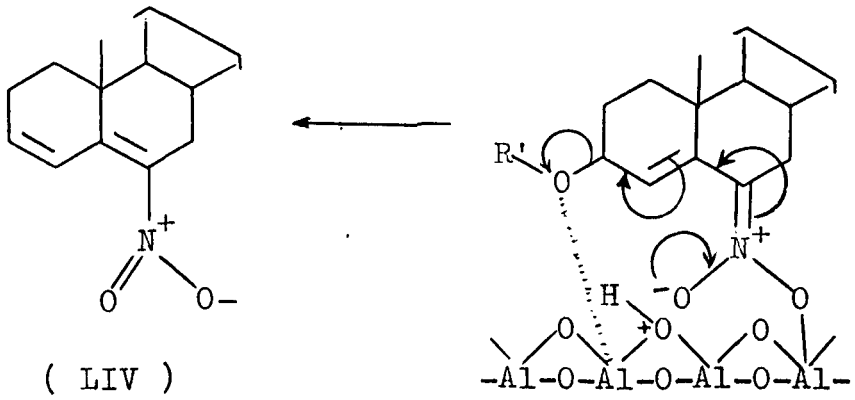
	R
(LVII)	OH
(LVIII)	OAc

(LIX)

Scheme - 3a

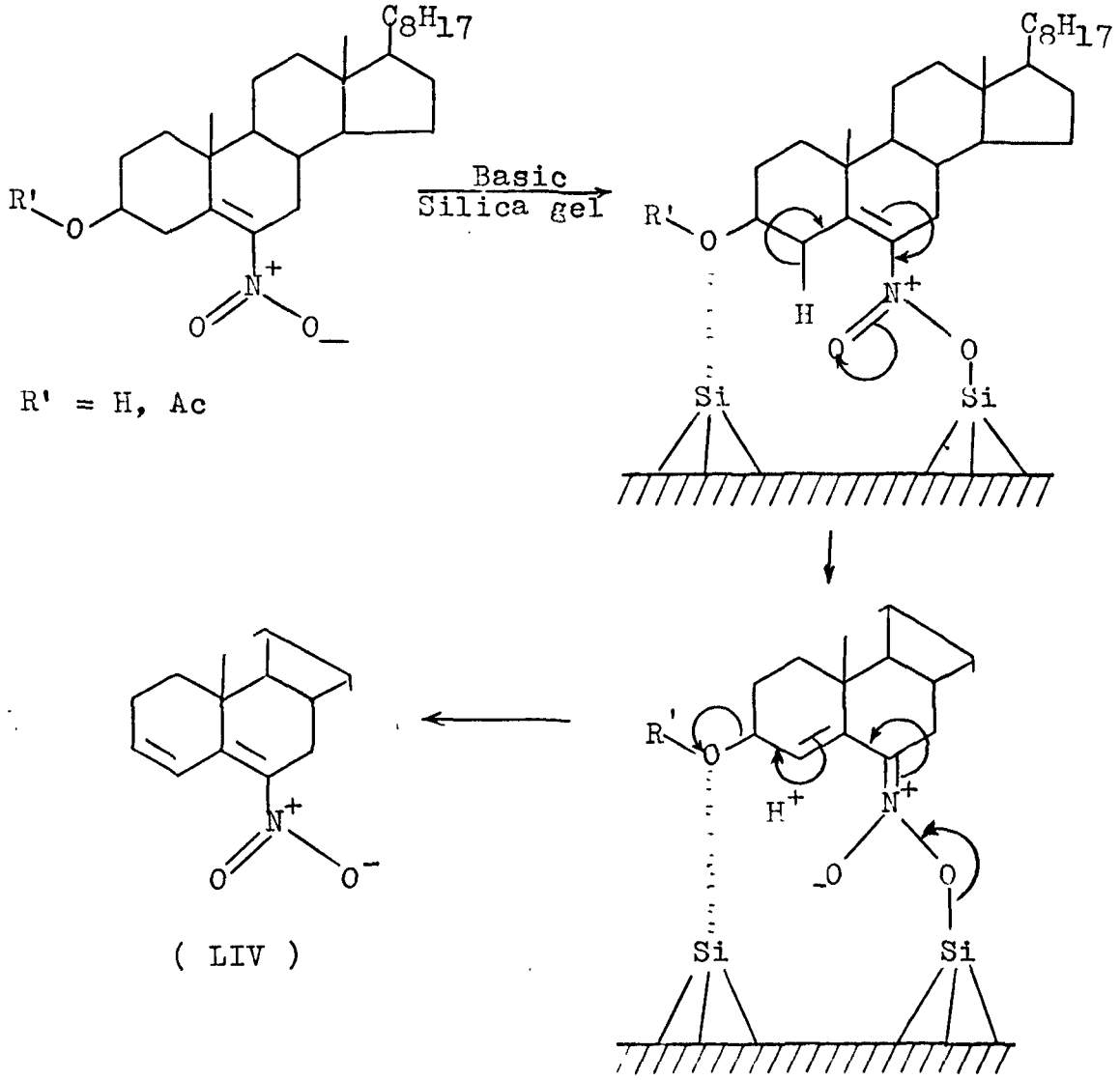


R' = H, Ac



(LIV)

Scheme - 3b



R' = H, Ac

INTRODUCTION

Steroids are widely distributed in nature and play an important role in the vital activity of living organisms. They constitute a family of substances critically important to plant and animal life. Steroids include the adrenal cortical hormones, the sex hormones, some of the vitamins, plant and animal sterols. This array of substances, though so alike chemically that it is often difficult to tell them apart, exhibit a prodigious range of different activities.

In recent past, the chemistry of steroids has provided one of the most interesting research areas for organic chemists. The first phase of steroidal research was mainly concerned with the isolation of steroids from natural sources, their structure elucidation and biochemical studies. These researches resulted in the realization of the fact that naturally occurring oxa- and azasteroids, such as steroidal alkaloids are endowed with pronounced and specific biological activities. This prompted the organic chemists to undertake synthetic modifications of natural steroids to enhance selectively certain parameters of their biological activity. Organic chemists working in this field have struck with great

success with fascinating results which have encouraged them for stimulated research activity in this area of steroids with unusual carbon framework and uncommon substituents at different positions in the steroid nucleus. Syntheses of new steroidal analogues and their pharmacological testing have now become a major preoccupation with organic chemists and continue to fascinate them the world over.

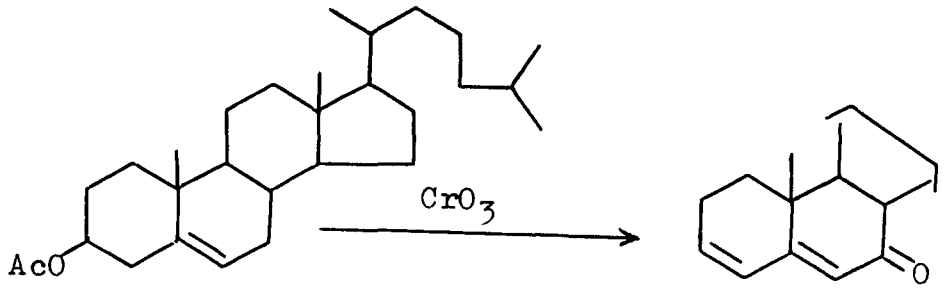
Our laboratory, concerned mainly with the syntheses of steroidal compounds and their identification, has reported the preparation of a number of hetero steroids. The present work is an attempt to explore mainly the preparation and reactions, mechanistic and stereochemical aspects, of steroidal nitro olefins which are recognised as potentially versatile and unique synthetic intermediates for the development of scientific methodology of synthetic steroids. We have also undertaken the synthesis of certain aminosterols in the cholestane series which are useful as anaesthatics, anticonvulsant and antiarrythmic drugs.

Part-One

Oxidation of Steroidal Nitro Olefins

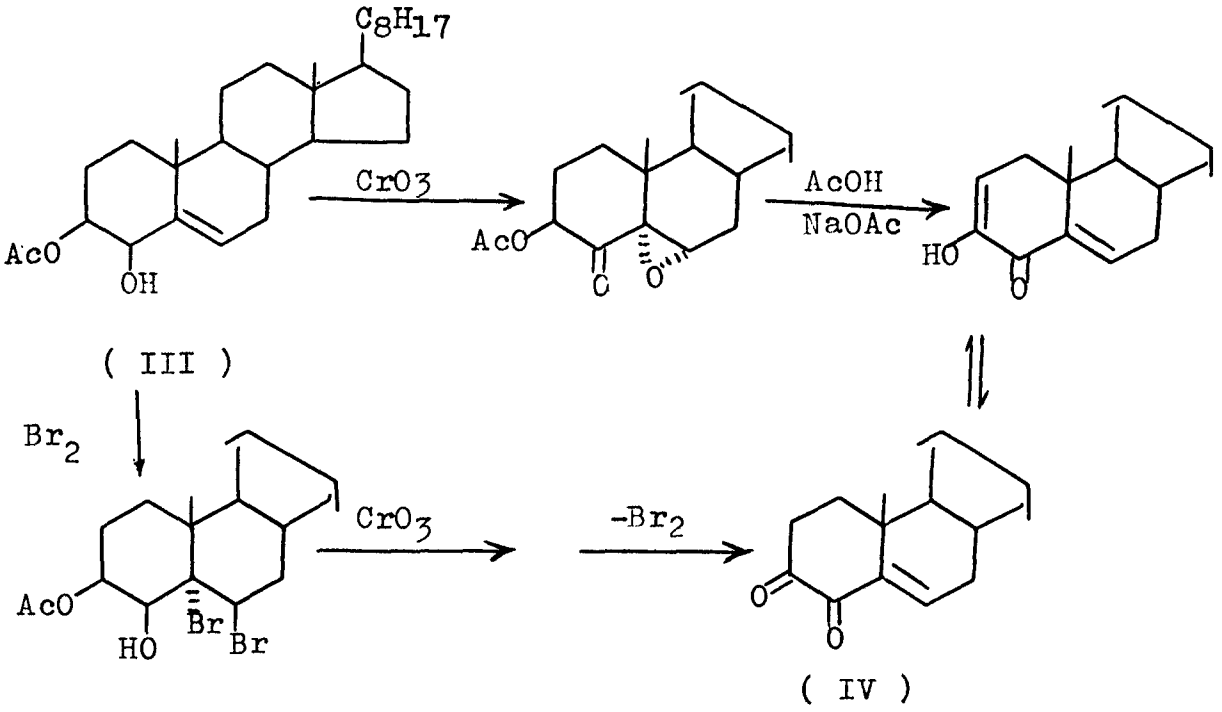
THEORETICAL

Chromium (VI) oxidation of carbon-carbon double bond can lead to the formation of a large variety of compounds including epoxides, α-glycols, α-ketals and other cleavage products. In addition, oxidation of allylic carbon hydrogen bond is often observed. Windaus and Naggatz[1] reported the oxidation of cholesteryl acetate (I) with chromic acid in acetic acid solution which on elimination of acetic acid afforded cholesta-3,5-dien-7-one (II).

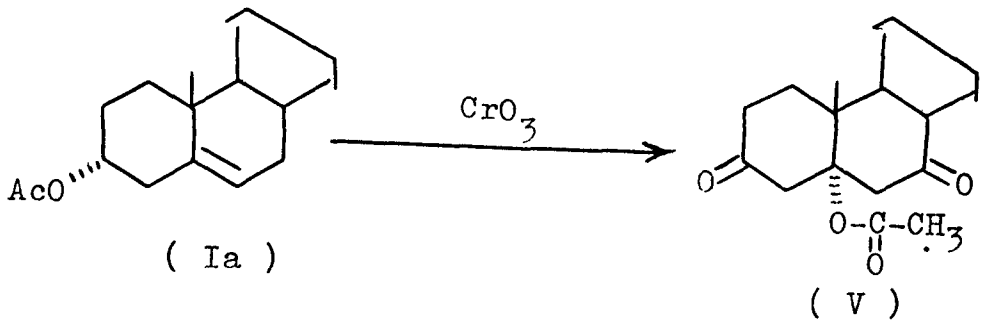


(I) (II)

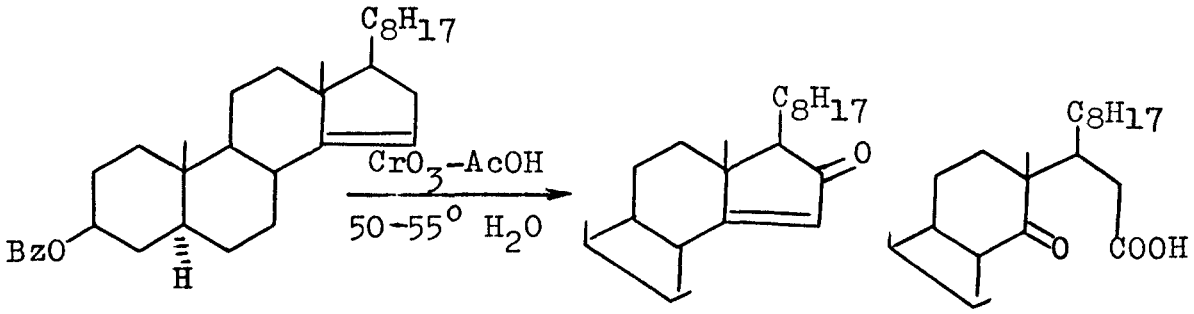
Petrow and Starling[2] found a new method for the preparation of diosphnol (α-diketone) (IV) consisting of mild oxidation of the 3β-acetoxy-4-hydroxycholest-5-ene (III) to diosphnol (IV). Its structure was given by Fieser et al.[3]



Fieser et al.[4] identified an oxidation product obtained by Windaus and Naggatz[1] in 1939, by chromic acid oxidation of epicholesteryl acetate (Ia)as 5-acetoxy-5α-cholestan-3,7-dione(V) resulting from the intermolecular C3-C5 acyl migration.

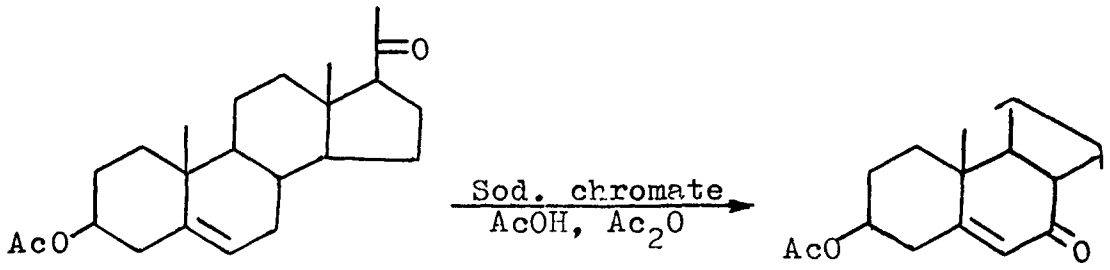


Chromic acid oxidation of Δ^{14}-cholesten-3β-ol benzoate (VI) gave 16-keto-Δ^{14}-cholesten-3β-ol-benzoate (VII) and the ketocarboxylic acid (VIII)[5].



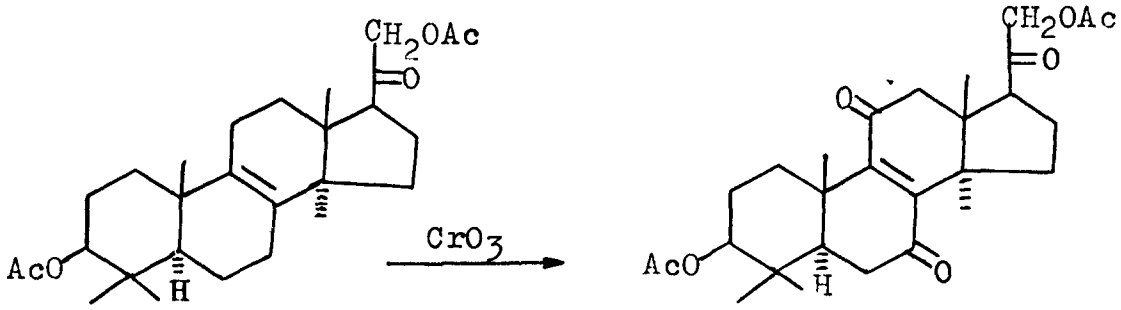
(VI) (VII) (VIII)

α,β-Unsaturated ketones have been obtained in good yield from steroidal alkenes when they were subjected to oxidation by chromic acid in acetic acid solution . Marshall et al.[6] have reported the introduction of a carbonyl group at C7 position of pregnenolone acetate (IX) by use of sodium chromate in acetic acid-acetic anhydride solution. This reaction can also be accomplished by t-butyl chromate in CCl_4 solution containing acetic acid and acetic anhydride.



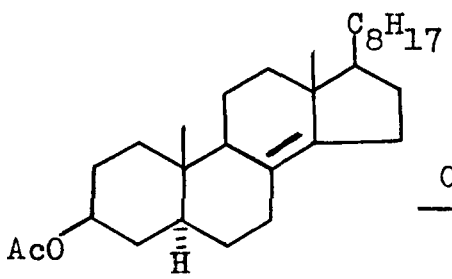
(IX) (X)

With Δ^8-pregnene derivatives, oxidation of allylic carbon-hydrogen bond is complicated by the possibility of carbonyl formation at both C7 and C11 positions. 3β,21-Diacetoxy-4,4,14α-trimethyl- Δ^8-5α-pregnene-20-one (XI) gives the triketone (XII) on oxidation with CrO_3-AcOH[7].

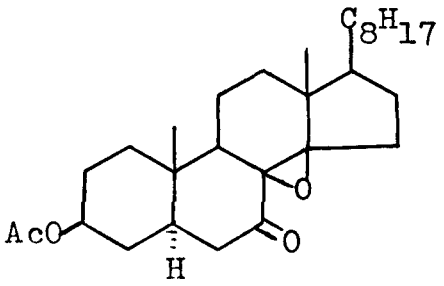


(XI) (XII)

Wintersteiner and Moore[8] obtained five products (XIV-XVIII) in varying yields when they oxidized α-(Δ^{8-14})-cholesteryl acetate (XIII) with CrO_3-AcOH.



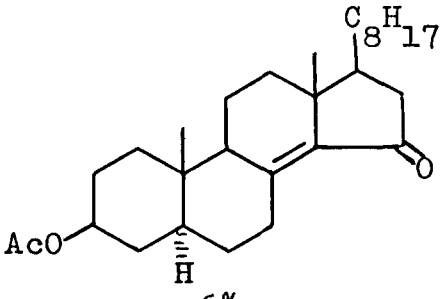
CrO_3-AcOH



+

16%

(XIII) (XIV)



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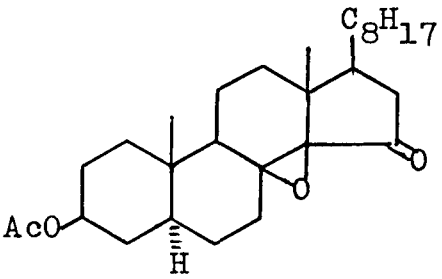
6%

(XV)



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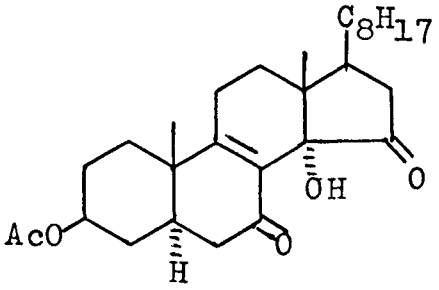
(XVI)



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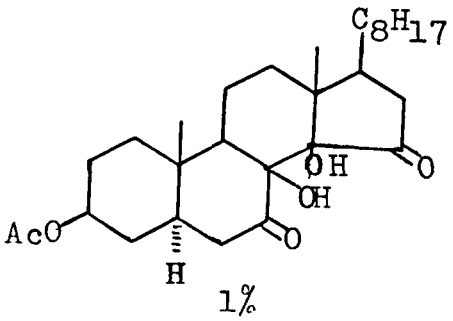
1%

(XVII)



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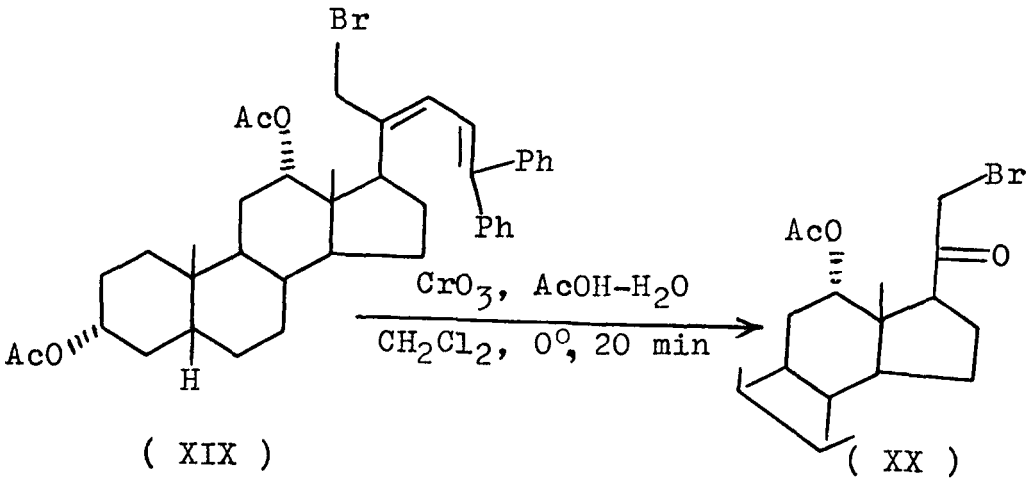
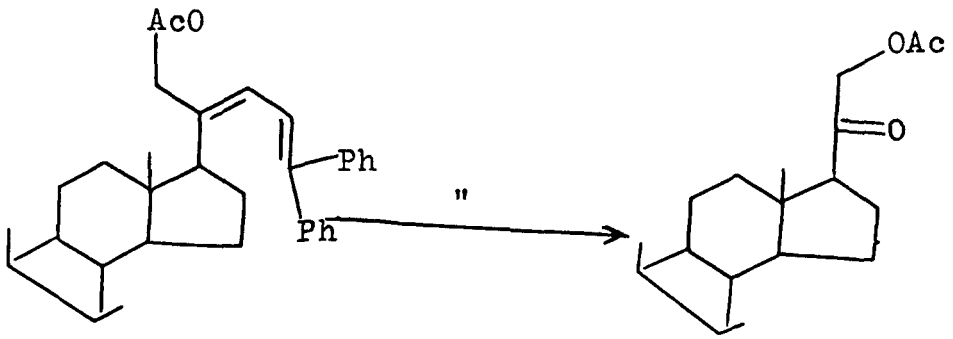
(XVIII)

Meystre and Wettstein[9] carried out the chromic acid oxidation of steroidal side chain double bond in order to obtain C20 ketosteroids (XX, XXII).

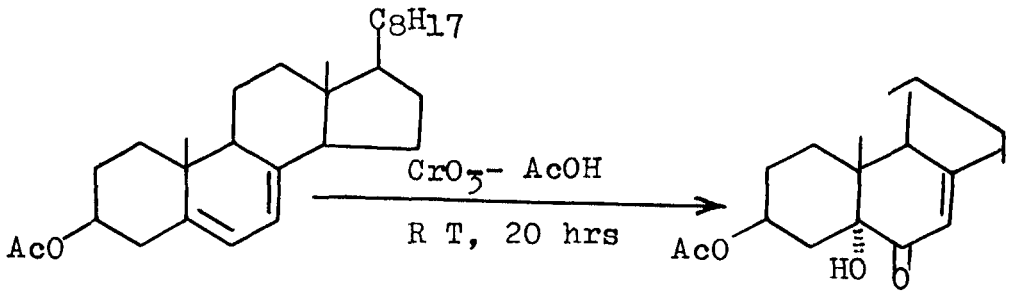


(XIX) (XX)



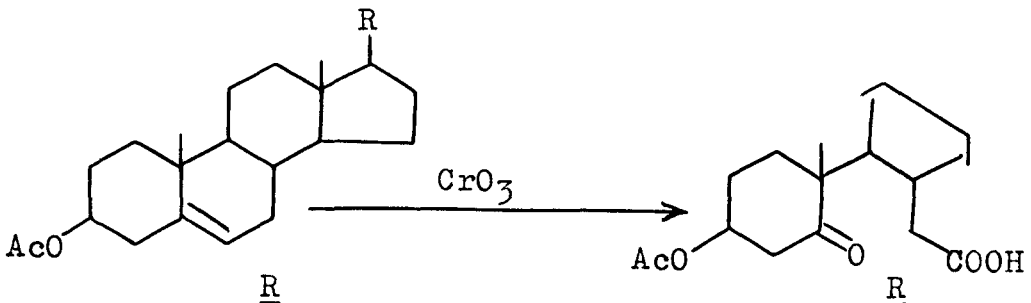
(XXI) (XXII)

Barton and Robinson[10] treated 3β-acetoxy cholesta-5,7-diene (XXIII) with chromic acid and obtained 3β-acetoxy-5-hydroxy-5α-cholest-7-en-6-one (XXIV) in 20% yield.



(XXIII) (XXIV)

Elks et al.[11] subjected 3β-acetoxycholest—5-ene (I) to chromic acid oxidation to get 5,6-seco product. Similar oxidation of (XXV) gave similar cleavage product[12] (XXVII).

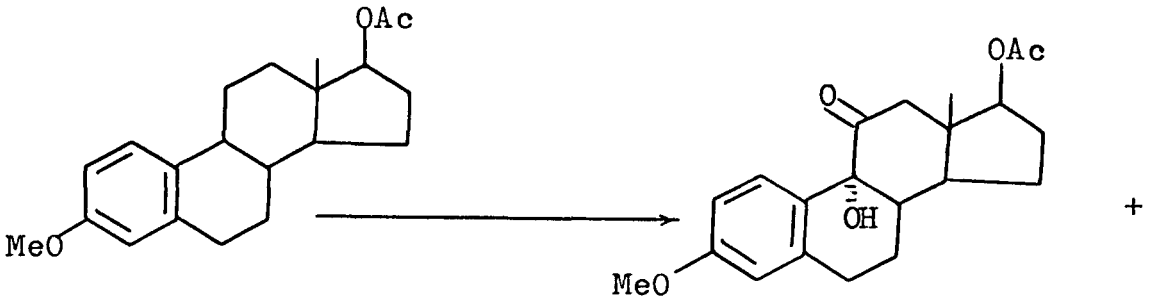


	R
(I)	C_8H_{17}
(XXV)	O

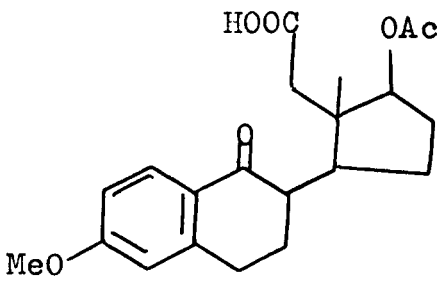
	R
(XXVI)	C_8H_{17}
(XXVII)	O

Suzuki[13] had claimed that the oxidative products of 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (XXVIII) are 17β-acetoxy-9α-hydroxy-3-methoxyoestra-1,3,5(10)-trien-

11-one (XXIX), 35% and seco-derivative, 17β-acetoxy-3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (XXX) in 45% yield.

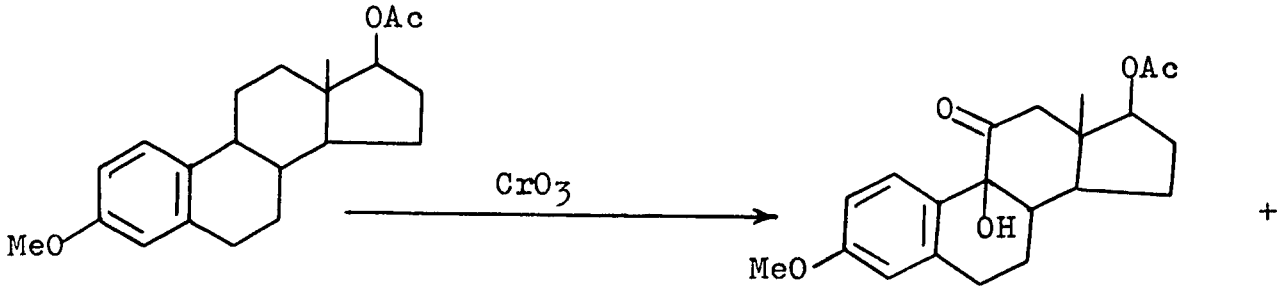


(XXVIII) (XXIX)

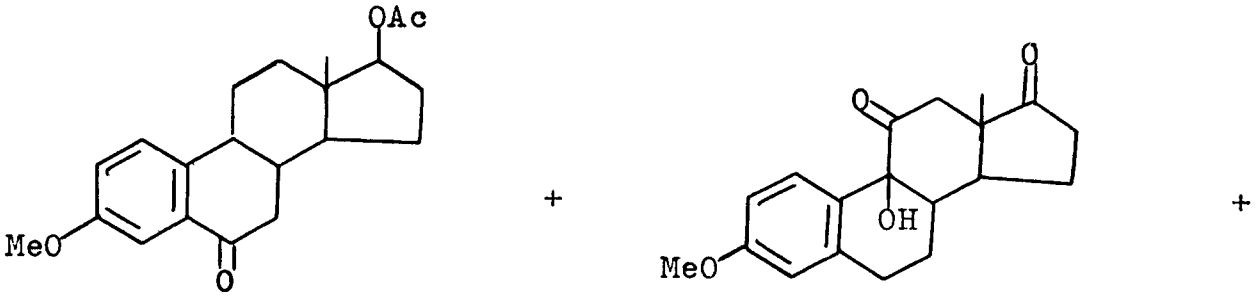


(XXX)

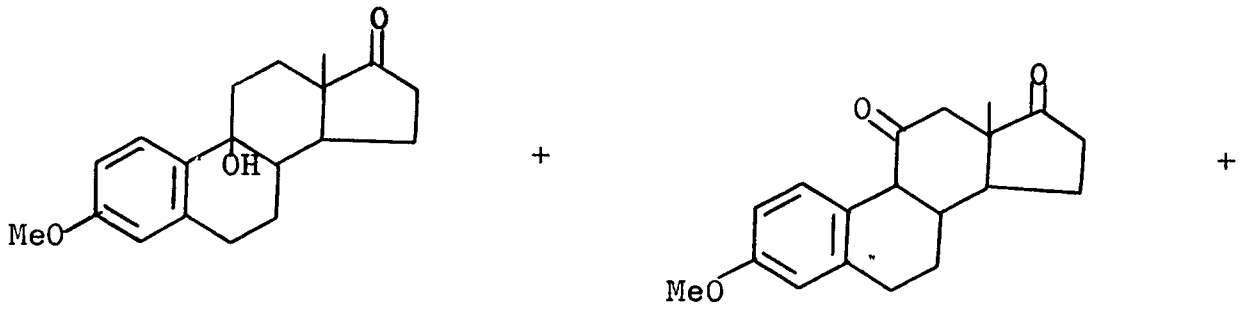
Cambie and Manning[14] reexamined the oxidation 3-methoxyoestra-1,3,5(10)-trien-17β-yl acetate (XXVIII) with chromium trioxide and reported the products (XXXI-XXXVII).



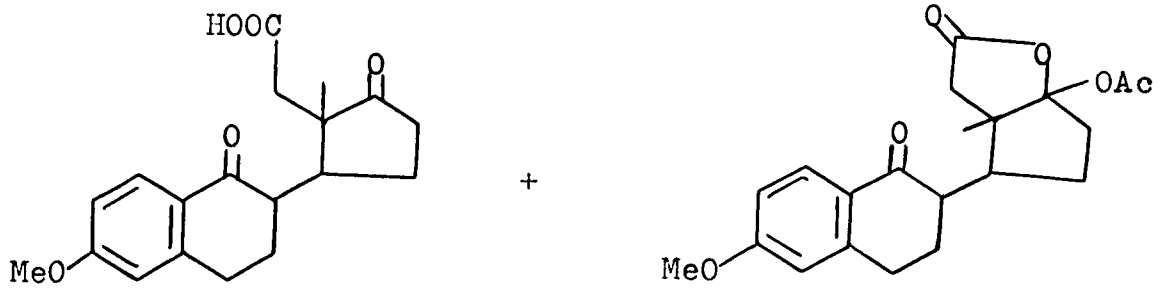
(XXVIII) (XXXI)



(XXXII) (XXXIII)

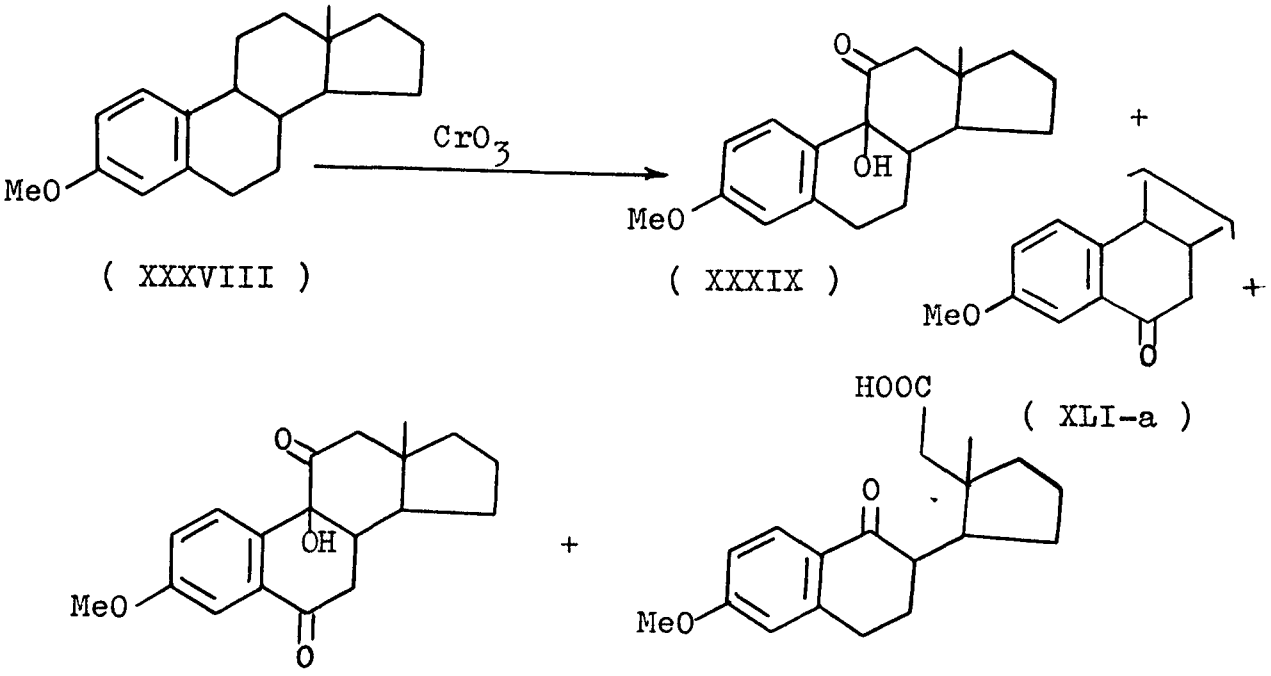


(XXXIV) (XXXV)



(XXXVI) (XXXVII)

During another oxidative study of 3-methoxyoestra-1,3,5(10)-triene (XXXVIII), Cambie et al.[15] obtained 9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-11-one (XXXIX), 9β-hydroxy-3-methoxyoestra-1,3,5(10)-trien-6,11-dione (XL), 3-methoxy-9-oxo-9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (XLI) and 3-methoxyoestra-1,3,5(10)-trien-6-one (XLI-a).

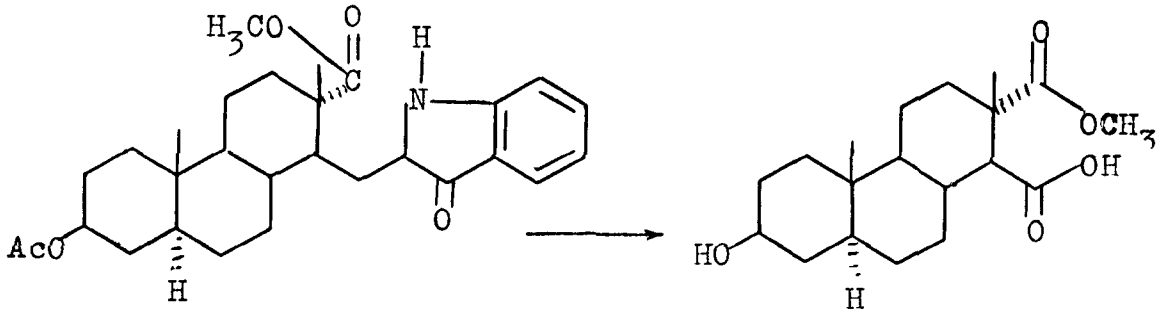


(XXXVIII) (XXXIX) (XLI-a)

(XL) (XLI)

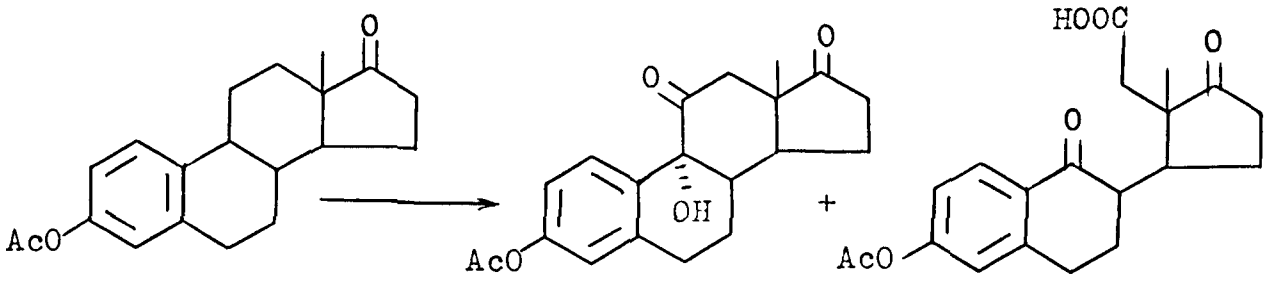
Banerjee and Gut[16] carried out the oxidation of methyl 3β-acetoxy-16,17-seco-16-norandrostan-15(2'-indoxyliden)-17-oate (XLII) with chromium trioxide in acetic acid at room temperature for 16 hrs giving 3β-hydroxy-15,17-seco-D-

norandrostane-15,17-dioic 17-methyl ester (XLIII) in 75% yield. The reaction is stereospecific, consists of fewer steps and gives higher yield.



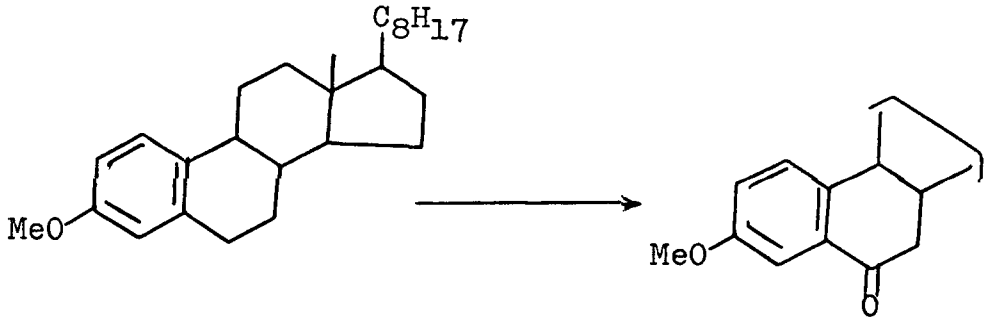
(XLII) (XLIII)

Cambie and Carlisle[17] carried out the chromic acid oxidation of 3-acetoxyoestra-1,3,5(10), 9(11)-tetraene-17-one (XLIV) in acetone at -18°. After reacetylation, 11,17-dioxooestra-1,3,5(10)-triene-3,9α-diol 3-acetate (XLV), and 3-acetoxy-9,17-dioxo9,11-seco-oestra-1,3,5(10)-trien-11-oic acid (XLVI) were isolated from neutral and acidic fractions respectively.



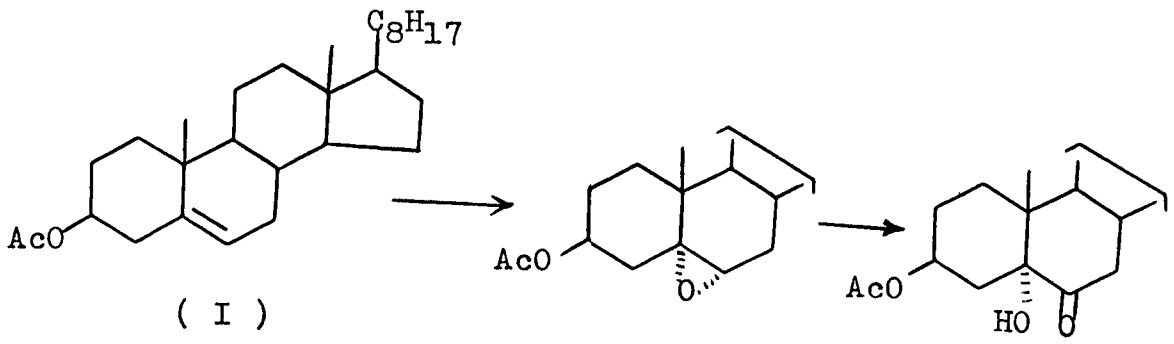
(XLIV) (XLV) (XLVI)

Cambie et al.[18] carried out the chromic acid oxidation of 3-methoxycholesta-1,3,5(10)-triene (XLVII) and obtained 6-oxo derivative (XLVIII) as major product.

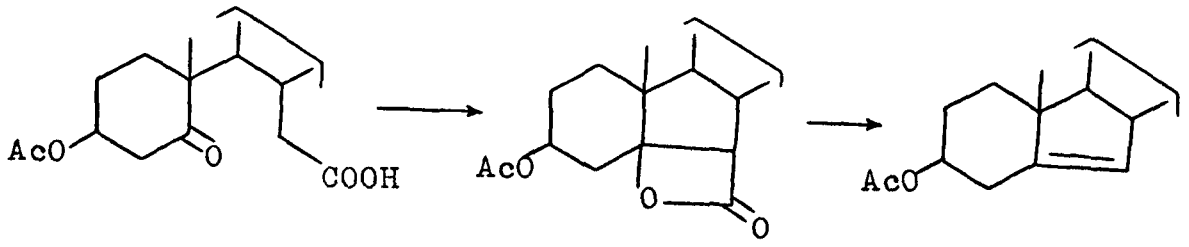


(XLVII) (XLVIII)

Schwartz and Juhasz[19] prepared 3β-hydroxy-B-nor-cholest-5-ene acetate (L) according to the reaction sequence given below.

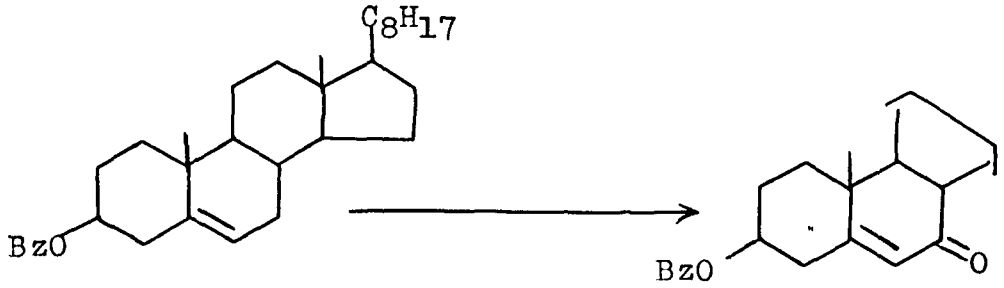


(I) (XLIX)

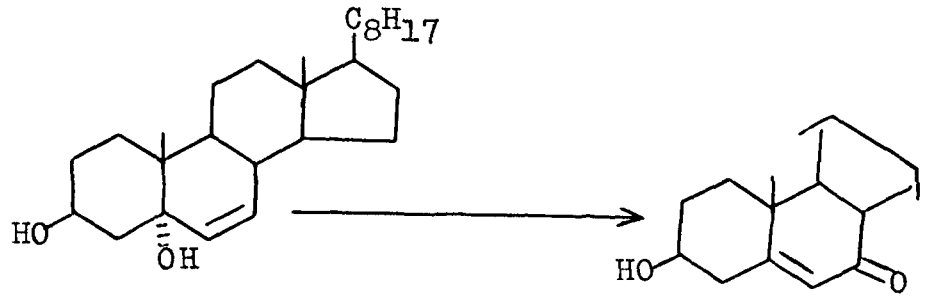


(L)

Recently[20] chromic anhydride-3,5-dimethylpyrazole complex has been utilized for the oxidation of cholesteryl benzoate (LI) to Δ^5-7-ketone (LII). The oxidation of Δ^6-cholesten-3β, 5α-diol (LIII) with same reagent also gave Δ^5-7-ketone (LIV).

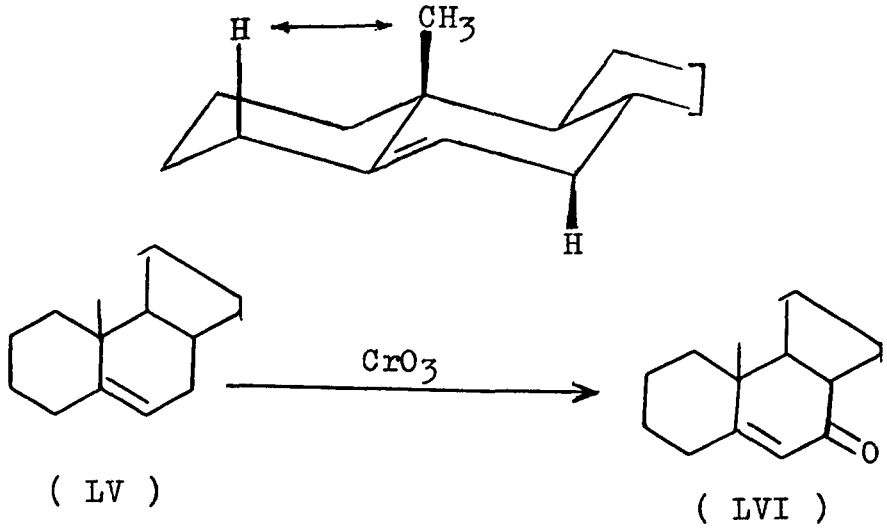


(LI) (LII)



(LIII) (LIV)

In cholest-5-ene (LV) there are two conformationally inflexible sites of allylic hydrogens (C4 and C7). It is to be expected that axial hydrogens will be preferentially abstracted to equatorial hydrogens of more favourable stereoelectronic situation with the developing p-orbital and the π system[22]. In the steroid case, the axial hydrogen on C4 lies above the plane of steroid molecule and the approach of the chromium species would be hindered by the angular methyl group at C10. The axial hydrogen at C7 being below the plane of molecule is free from such steric interferences and the reaction occurs at this position to yield 5-cholesten-7-one (LVI). Similar results are obtained in all related rigid systems i.e. oxidation occurs in the ring holding the double bond[23-25].



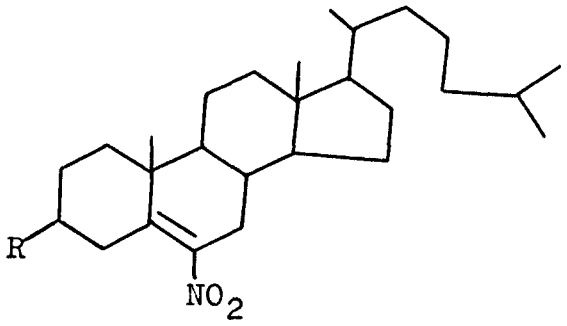
(LV) (LVI)

DISCUSSION

The oxidation of an olefin to an α,β-unsaturated ketone has been utilized in the synthesis and in the transformation of natural products. In most of the cases, chromium (VI) has been the oxidant and varying results have been obtained depending upon the specific chromium (VI) reagent used and conditions employed[26-32]. The conditions used most often have been chromium (VI) in acetic acid but in recent years t-butyl chromate[27-29] has been employed with varying degree of success. With the latter reagent, the reaction is usually run at an elevated temperature (60-80°) for an extended period of time (10-70 hrs). More recently, CrO_3 in pyridine[31] was employed at room temperature for 30 days.

We have made an attempt to carry out the chromium (VI) oxidation of some of the easily accessible steroidal nitro-olefins in order to see the effect of nitro group on the course of oxidation of the olefins. The nitroolefins selected for the present study were 6-nitrocholest-5-ene (LVII), 3β-chloro-6-nitrocholest-5-ene (LVIII) and 3β-acetoxy-6-nitrocholest-5-ene (LIX) and the reagent used was chromic acid. The oxidation resulted in the formation of some of the

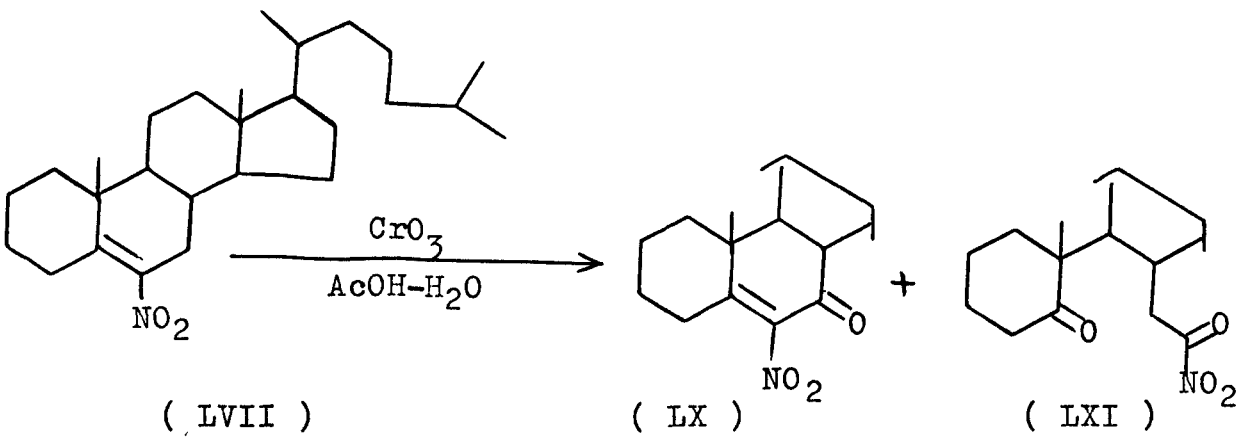
interesting products which were identified on the basis of their spectral and chemical properties.



	R
(LVII)	H
(LVIII)	Cl
(LIX)	OAc

Reaction of 6-nitrocholest-5-ene (LVII) with chromic acid

6-Nitrocholest-5-ene (LVII) was treated with chromic acid in acetic acid at 60-80°C. After the usual work up of reaction mixture and chromatography over silica gel two compounds, m.p. 167-168° and 176-177° were obtained.



(LVII) (LX) (LXI)

Characterization of compound, m.p. 167-168° as 6-nitrocholest-5-en-7-one (LX)

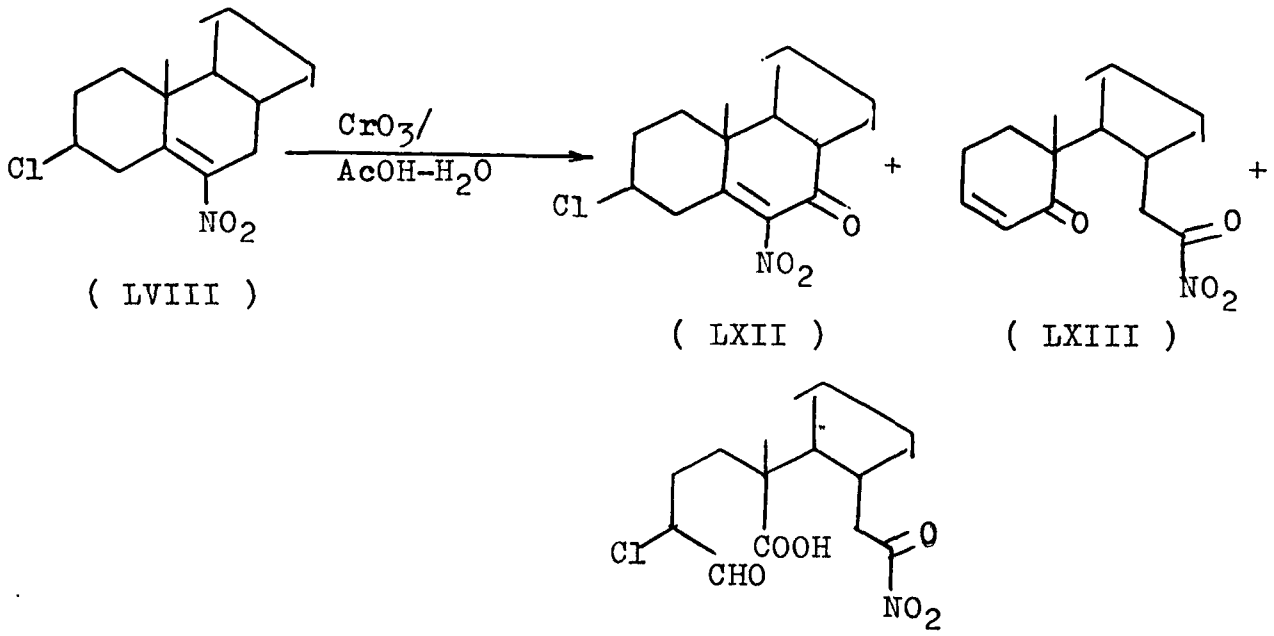
The compound m.p. 167-168° was analysed correctly for $C_{27}H_{43}NO_3$ indicating the addition of one oxygen atom to the parent compound (LVII). The IR spectrum of the compound showed strong bands at 1690 (C=C-C=O), 1540 and 1390 cm^{-1} ($C-NO_2$).[34] It was evident from IR spectral values that the compound has undergone allylic oxidation to give an α,β-unsaturated carbonyl compound. The bands at 1540 and 1390 cm^{-1} are indicative of the fact that the nitro group at C6 remains unaffected during the course of reaction. The presence of carbonyl group at C4 rather than at C7 was ruled out because of the fact that the ring B containing the double bond (C5=C6) is more susceptible towards allylic oxidation.[23-25] The structure was further supported by UV spectrum which absorbed at λ 258 nm for $-C=\underset{\underset{NO_2}{|}}{C}-C=O$ group.[35] The NMR spectrum of the compound was not very significant from the structure elucidation point of view. It showed signals at δ 1.3 (C10β-CH_3), 0.7 (C13β-CH_3), 0.95, 0.90 and 0.75 (other methyl protons). On the basis of above discussion the compound was characterized as 6-nitrocholest-5-en-7-one (LX).

Characterization of the compound, m.p. 176-177° as 5,6-seco-6-nitro-5,6-diketocholestane (LXI)

The compound, m.p. 176-177° was analysed correctly for $C_{27}H_{45}NO_4$ indicating the addition of two oxygen atoms to the parent compound (LVII). The IR spectrum of the compound exhibited two strong absorption bands at 1710 and 1690 cm^{-1} indicating thereby the presence of two carbonyl groups. The fact that nitro group remains intact in the final product is established by two strong bands 1535 and 1370 cm^{-1}. The NMR spectrum of the compound was not significant so far as the characterization of the compound was concerned. It displayed a broad multiplet at δ 2.3 integrating for four methylene protons (C4-$\underline{H}_2$ and C7-$\underline{H}_2$) adjacent to two carbonyl groups. Other signals were observed at δ 1.3 (C10β-$C\underline{H}_3$), 0.7 (C13β-$C\underline{H}_3$), 1.0 and 0.9 (other methyl protons). The above spectral properties revealed that the compound was 5,6-seco-6 nitro-5,6-diketocholestane (LXI)

Chromic acid oxidation of 3β-chloro-6-nitrocholest-5-ene (LVIII)

The oxidation of 3β-chloro-6-nitrocholest-5-ene (LVIII) was carried out as described earlier. Usual work up and column chromatography of the reaction mixture provided three compounds, two solids with m.p . 155° and 170° and an oil.



(LVIII) (LXII) (LXIII)

(LXIV)

Characterization of the compound m.p. 155° as 3β-chloro-6-nitrocholest-5-en-7-one (LXII)

The compound m.p. 155° was analysed correctly for $C_{27}H_{42}NO_3Cl$. It gave positive Beilstein test for chlorine. The IR spectrum of the compound showed strong bands at 1690 (C=C-C=O), 1540 and 1390 (C-NO_2) and 730 cm^{-1} (C-Cl).[31] Both, the presence of nitro group and the α,β-unsaturation were confirmed on the basis of IR spectrum, which was further supported by UV spectrum, which gave an absorption maxima at λ 251 nm for the group -C=C(NO$_2$)-C=O.[35] The NMR spectrum of the compound showed signals at δ 3.78 (m, C3α-H, $W\frac{1}{2}$ = 17 Hz, axial),[33] 1.3 (C10β-CH_3), 0.68 (C13β-CH_3), 0.9 and 0.83 (other methyl protons).

On the basis of above spectral properties compound m.p. 155° was characterized as 3β-chloro-6-nitrocholest-5-en-7-one (LXII).

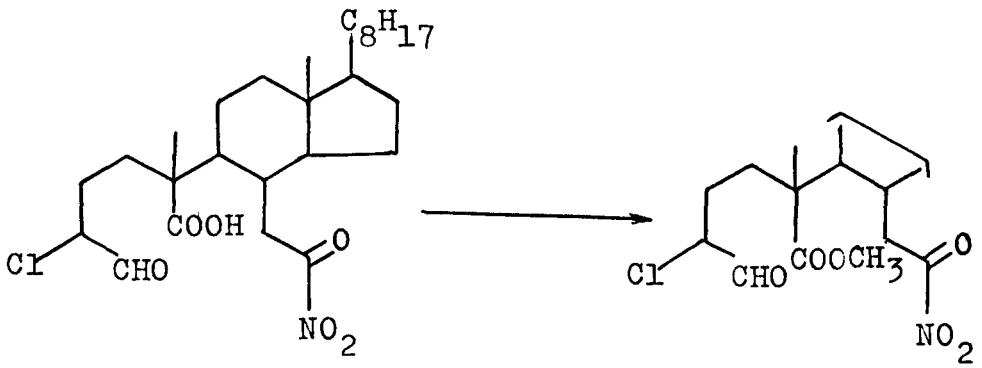
Characterization of the compound, m.p. 170° as 5,6-seco-6-nitro-5,6-diketocholest-3-ene (LXIII)

The compound m.p. 170° was analysed for $C_{27}H_{43}NO_4$. It gave negative Beilstein test which indicated the loss of chlorine atom from C3. The IR spectrum of the compound showed strong band at 1670-1680 cm^{-1} which was a combination of two bands. It indicated the presence of one α,β-unsaturated carbonyl group (C5 carbonyl group) and another ketone attached to nitro group (C6 carbonyl group), carbon-carbon double bond was represented by a band at 1620 cm^{-1}. The two strong bands at 1535 and 1390 cm^{-1} contributed to the existance of the nitro group in the compound. The UV spectrum of the compound showed an absorption band at λ 230 nm which supported the presence of α,β-unsaturated carbonyl function in the compound[35]. The NMR spectrum of the compound displayed a multiplet at δ 6.9 for C3 proton and a doublet at δ 6.1 for C4 proton. Methyl proton signals were observed at δ 1.2 (C10β-$C\underline{H}_3$), 0.7 (C13β-$C\underline{H}_3$), 1.0, 0.93 and 0.83 (other methyl protons). On the basis of above discussion the structure of the compound was assigned as 5,6-seco-6-nitro-5,6-diketo-cholest-3-ene (LXIII).

Characterization of the oily compound as 3-chloro-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane (LXIV)

The oily compound was analysed correctly for $C_{27}H_{46}NO_6Cl$. It gave positive Beilstein test. It was evident from elemental analysis that four oxygen atoms have been added to parent compound. The IR spectrum of the compound showed a broad band at 3500-3450 cm^{-1} for hydroxyl group. A very broad band for carbonyl stetching frequencies was observed at 1690-1730 cm^{-1} for ($-\underset{\underline{}}{\overset{O}{\overset{\|}{C}}}-H$, $-\underset{\underline{}}{\overset{O}{\overset{\|}{C}}}-OH$ and $-\underset{\underline{}}{\overset{O}{\overset{\|}{C}}}-NO_2$). The IR spectrum also displayed bands at 1520 and 1370 cm^{-1} characteristic of a nitro group. A band at 760 cm^{-1} confirmed the presence of chlorine atom in the compound. The NMR spectrum of the compound exhibited a broad signal at δ 10.6 for carboxyl proton (-COO$\underline{H}$). The signal disappeared on D_2O addition. A sharp singlet for one proton at δ 7.3 was assigned to an aldehyde proton present at C4. A multiplet at δ 3.78 for one proton is assigned to C3 -$\underline{H}$; $W\frac{1}{2}$ = 16 Hz) . Methyl proton signals were observed at δ 1.3 (C10β-C$\underline{H}_3$), 0.71 (C13β-C$\underline{H}_3$), 1.15 and 0.9 (other methyl protons). On the basis of above discussion the compound was characterized as 3—chloro-4,5:5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane (LXIV). Seco acid (LXIV) was converted to its methyl ester (LXV) m.p. 147°, on treatment with diazomethane. It was analysed for $C_{28}H_{48}NO_6Cl$. The IR spectrum of the methyl ester (LXV) was devoid of any hydroxyl absorption band indicating

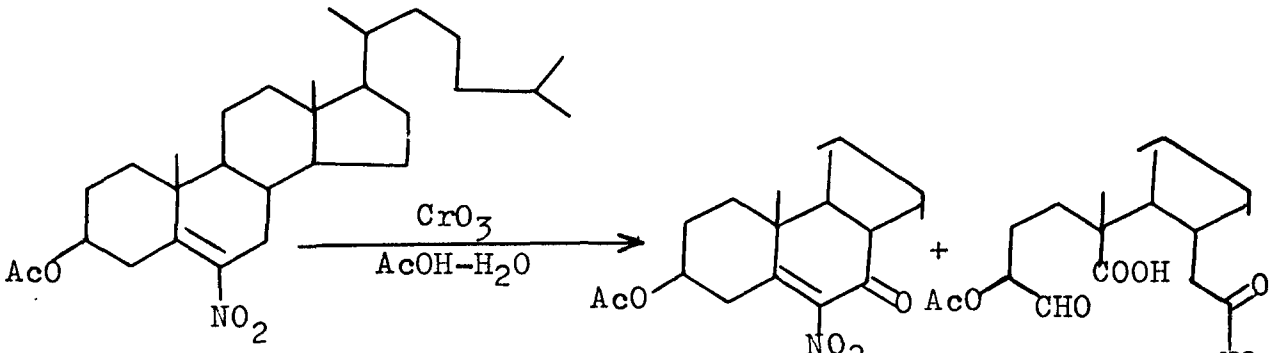
that the carboxyl group has been converted to methyl ester. A broad band of carbonyl absorption was exhibited at 1735 cm^{-1}. The nitro group was indicated by 1520 and 1360 cm^{-1} absorption bands. The NMR spectrum of the methyl ester (LXV) displayed an additional peak at δ 3.6 integrating for three protons of methyl group of the ester. The other significant observation was the disappearance of the carboxyl proton signal. Aldehydic proton was shown at δ 7.3 and a multiplet was observed for C3 proton at δ 3.7. Methyl signals were seen at δ 1.31 (C10β-$C\underline{H}_3$), 0.7 (C13β-$C\underline{H}_3$), 1.16 and 0.93 (other methyl protons). Thus the above compound was identified as methyl 3-chloro-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitrocholestane-10-carboxylate (LXV).



(LXIV) (LXV)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LIX) with chromic acid

The chromic acid oxidation of 3β-acetoxy-6-nitrocholest-5-ene (LIX) was carried out as described for 6-nitrocholest-5-ene (LVII). Usual work up of the reaction mixture followed by column chromatography over silica gel afforded two compounds, one solid m.p. 180° and the other an oil.



(LIX) (LXVI) (LXVII)

Characterization of the compound m.p. 180° as 3β-acetoxy-6-nitrocholest-5-en-7-one (LXVI)

The compound m.p. 180° was analysed for $C_{29}H_{45}NO_5$ indicating the addition of one oxygen atom in the compound (LIX). The IR spectrum of the compound showed a strong absorption band at 1730 cm^{-1} ascribed for carbonyl of acetate group. α,β-Unsaturated ketone function was indicated by a strong absorption at 1680 cm^{-1} and was further supported by a medium intensity band

at 1620 cm^{-1}. The presence of nitro group was shown by two strong absorption bands at 1525 and 1370 cm^{-1}. The compound exhibited an absorption maxima at 250 nm on its UV spectrum which further supported the presence of α,β-unsaturated ketone moiety in the molecule.[35] The NMR spectrum of the compound exhibited a multiplet at δ 4.6 ($W\frac{1}{2}$ = 18 Hz) for C3 axial proton[33] and a singlet for three protons at δ 2.12 accounted for methyl protons of acetate group. Methyl protons were displayed at δ 1.28 (C10β-CH_3), 0.65 (C13β-CH_3), 1.20, 0.86 and 0.80 (other methyl protons). The above spectral values therefore suggested the structure of the compound m.p. 180° as 3β-acetoxy-6-nitro-cholest-5-en-7-one (LXVI).

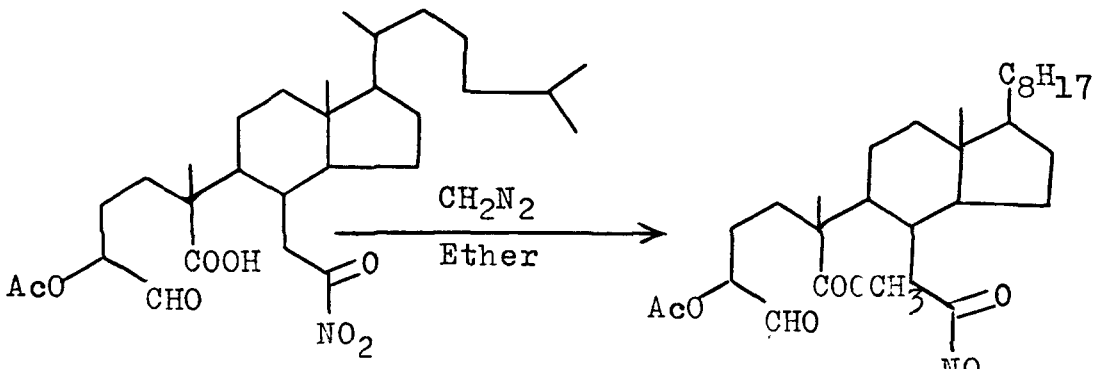
Characterization of the compond, an oil, as 3-acetoxy-4,5:5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane (LXVII)

The oily compound was analysed correctly for $C_{29}H_{47}NO_8$. It showed the addition of four oxygen atoms in the parent compound (LIX). The IR spectrum of the compound exhibited bands at 3500-3400 cm^{-1} (-OH) and a very broad band of carbonyl stretching frequencies at 1740-1690 cm^{-1} which was a combination of four bands indicating the presence of four carbonyl groups (-$CONO_2$, CH_3-COO, -CHO and -COOH) in the molecule. The bands at 1530 and 1370 cm^{-1} were assigned to nitro group.[34] The NMR spectrum of the compound displayed a broad singlet at δ 10.26

which was ascribed for carboxyl proton. It disappeared on exchange with D_2O. A sharp singlet was observed at δ 7.35 integrating for one proton and was assigned to an aldehydic proton. The multiplet at δ 4.6 ($W\frac{1}{2}$ = 17 Hz) was due to (H-C3-C1) proton . The three protons of acetate methyl group were seen at δ 2.0 as singlet. Methyl signals were displayed at δ 1.23 (C10β-CH_3), 0.73 (C13β-CH_3), 1.16 and 0.95 (other methyl protons). On the basis of forgoing discussion it was evident that the compound besides having acetate function, contained a carbonyl group, a carboxyl group an aldehyde function and a nitro group. All these were convincingly accommodated in the structure of the oily compound as 3-acetoxy-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carooxy-cholestane (LXVII).

The compound (LXVII) was converted to its methyl ester (LXVIII), m.p. 134°, on treatment with diazomethane, and was analysed for $C_{30}H_{49}NO_8$. The IR spectrum of the ester had no absorption in hydroxyl group range suggesting that -OH group is absent in the compound. A broad and strong absorption band at 1735-1725 cm^{-1} was observed for four carbonyl groups (CH_3COO-, -$CONO_2$, -CHO and -$COOCH_3$). The nitro group showed its absorption at 1520 and 1360 cm^{-1}. The NMR spectrum of the compound (LXVIII) displayed a singlet for three protons at δ 3.7 for methyl group of the ester. A sharp singlet for one proton at δ 7.3 was ascribed for aldehydic proton. Methyl

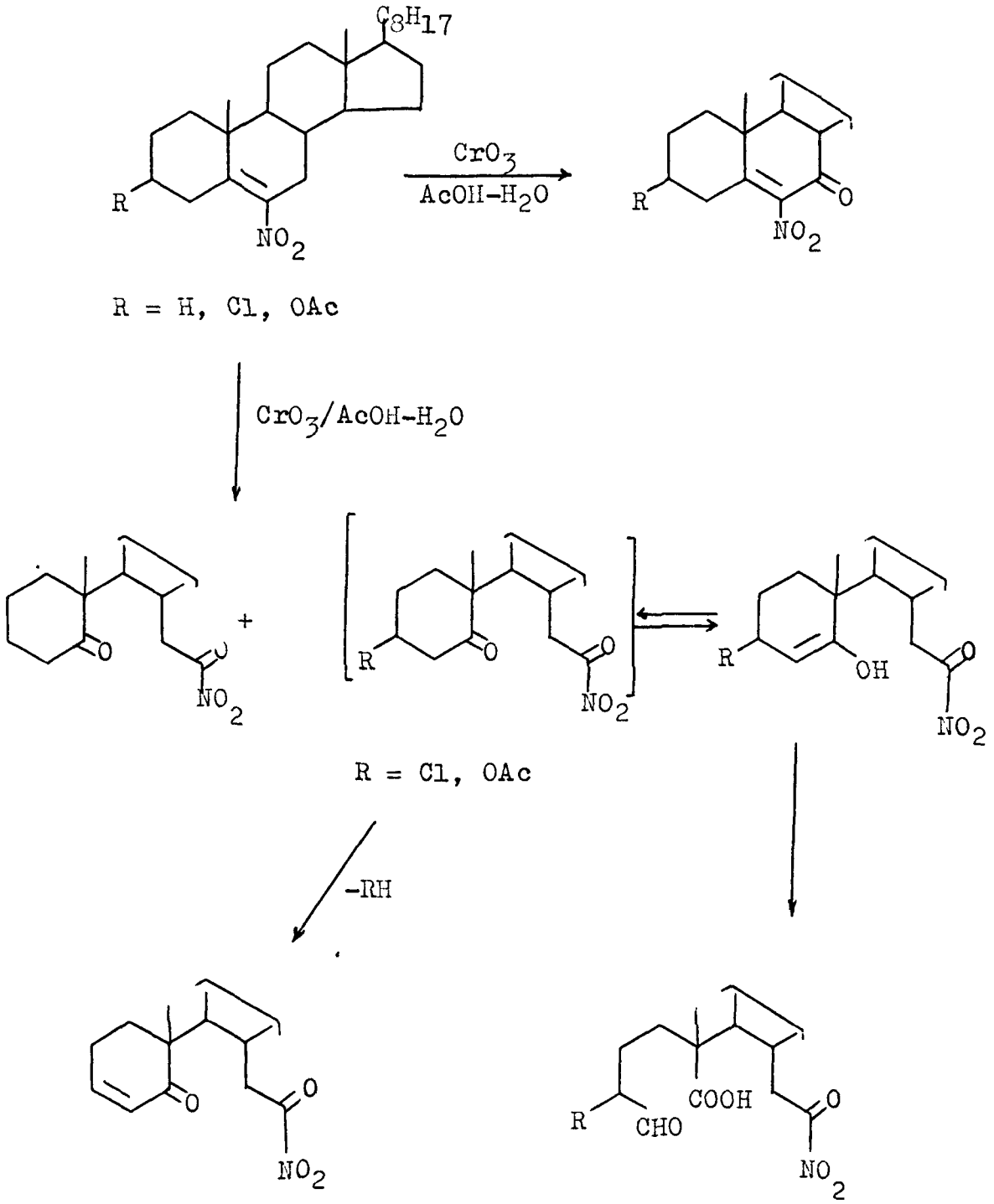
protons of acetate group were displayed at δ 2.1 as singlet. A multiplet at δ 4.7 was assigned to C3-proton. Methyl signals were seen at δ 1.25 (C10β-$C\underline{H}_3$), 0.74 (C13β-$C\underline{H}_3$), 1.16 and 0.97 (other methyl protons). The above compound (LXVIII) was therefore identified as methyl 3-acetoxy-4,5:5,6-bis-seco-3-formyl-6-keto-6-nitrochlolestane-10-carboxylate (LXVIII).



(LXVII) (LXVIII)

The formation of the cleavage products which were obtained during oxidation of nitroolefins (LVII, LVIII and LIX) can be explained according to scheme-1 given below:-

Scheme - 1


C_8H_{17}
R
NO_2
CrO_3
$AcOH-H_2O$
O
R = H, Cl, OAc
$CrO_3/AcOH-H_2O$
+
R = Cl, OAc
-RH
OH
COOH
CHO

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (IR) were determined in KBr with a Perkin-Elmer 237 spectrophotometer. IR values are given in cm^{-1}. UV spectra were run on Pye Unicam PU 8800 UV/VIS spectrophotometer and the values given in nm. Nuclear magnetic resonance spectra were run in $CDCl_3$ on a Varian A-60 instrument with tetramethylsilane (TMS) as the internal standard. The NMR values were given in ppm (δ). Thin layer chromatographic (TLC) plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate (Na_2SO_4) was used as drying agent. The abbreviations "s, d, t, m and br" denote "singlet, doublet, triplet, multiplet and broad" respectively.

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened the mixture was gently

heated at a temperature 50-60° on a water bath for 1 hour and then poured on to crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice cooled water and air dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (95.5 g), m.p.95-96° (reported[36], m.p. 96-97°).

Cholest-5-ene (LV)

3β-Chlorocholest-5-ene (10 g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (10 g) was added to the solution with continuous stirring over a period of 8 hrs. The reaction mixture was warmed occasionally. When all the sodium metal was dissolved, the reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand over night. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. The crude material was recrystallized from acetone to provide cholest-5-ene as cubes (8.3 g), m.p. 94° (reported[37], m.p. 95°).

6-Nitrocholest-5-ene (LVII)

A suspension of finely powdered cholest-5-ene (6 g) in glacial acetic acid (50 ml) was vigorously stirred at room temperature and treated with nitric acid (15 ml; d, 1.5) followed by the addition of sodium nitrite (3 g) over a period of 1 hr.

The reaction mixture was poured into cold water and the yellow product thus obtained was extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (10%) untill washings were pink and again with water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired compound as an oil which was crystallized from ethanol as leaflets (4.5 g), m.p. 119-120° (reported[38], m.p. 120-121°).

3β-Chloro-6-nitrocholest-5-ene (LVIII)

To a well stirred solution of 3β-chlorocholest-5-ene (12 g) in glacial acetic acid (80 ml) and nitric acid (25 ml; d, 1.52) at temperature below 20° was added sodium nitrite (6.0 g) gradually over a period of 2 hrs. After the complete addition of sodium nitrite, the mixture was further stirred for about 1 hr. Ice cooled water (200 ml) was added and the yellowish solid thus separated was filtered and air dried, the desired product was recrystallized from methanol as needles (8.3 g), m.p. 151-152° (reported[39], m.p. 153°).

3β-Acetoxycholest-5-ene (I)

A mixture of cholesterol (100 g), purified pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a steam bath for two hrs. After usual work up

procedure the crude acetate was crystallized from acetone as fine needles (94.0 g), m.p. 115-116° (reported[40], m.p. 116°).

3β-Acetoxy-6-nitrocholest-5-ene (LIX)

3β-Acetoxycholest-5-ene (10 g) was covered with nitric acid (d, 1.52; 250 ml) and sodium nitrite (10 g) was gradually added over a period of 1 hr with continuous stirring, slight cooling was also affected during the course of reaction and stirring was continued for additional 2 hrs, when a yellow spongy mass separated on the surface of the mixture. The whole mass was extracted with ether and worked up in usual manner. The removal of the solvent provided the nitro compound as an oil which was crystallized from methanol (6.5 g), m.p. 103° (reported[41], m.p. 102-104°).

Chromic acid oxidation of 6-nitrocholest-5-ene (LVII): 5,6-seco-6-nitro-5,6-diketocholest-5-en-7-one (LXI) and 6-nitrocholest-5-en-7-one (LX)

The compound (LVII) (5 g) was added to glacial acetic acid (100 ml) and to this a solution of chromic acid was added dropwise over a period of 8 hrs with stirring at 60-70°C. After completion of the reaction, the reaction mixture was diluted and washed with water several times and extracted with ether and dried over anhydrous sodium sulphate. Evaporation

of the solvent gave a residue which was chromatographed over silica gel (100 g). Elution with light petroleum-ether (20:1) afforded 6-nitrocholest-5-en-7-one (LX), recrystallized from light petroleum (1.00 g), m.p. 167-168°.

Analysis Found : C, 75.41; H, 10.03; N, 3.25

$C_{27}H_{43}NO_3$ requires : C, 75.52; H, 10.02; N, 3.26%

UV : λ 258 nm.

IR : $\nu_{max.}$ 1690 (-C=C-C=O), 1540 and 1390 cm^{-1} ($C-NO_2$).

^{1}H-NMR : δ 1.3 (C10β-CH_3), 0.7 (C13β-CH_3), 0.95, 0.9 and 0.75 (other methyl protons).

Further elution with light petroleum-ether (3:1) afforded 5,6-seco-6-nitro-5,6-diketocholestane (LXI) recrystallized from light petroleum (1.15 g), m.p. 176-177°.

Analysis Found : C, 70.20; H, 10.04; N, 3.15

$C_{27}H_{45}NO_4$ requires : C, 70.24; H, 10.06; N, 3.19%

IR : $\nu_{max.}$ 1710 (C=O), 1690 ($-\overset{O}{C}-NO_2$), 1535 and 1370 cm^{-1} ($C-NO_2$).

^{1}H-NMR : δ 2.3 (m, C4-H_2 and C7-H_2), 1.3 (C10β-CH_3), 0.70 (C13β-CH_3), 1.0 and 0.9 (other methyl protons).

<u>Chromic acid oxidation of 3β-chloro-6-nitrocholest-5-ene (LVIII): 3β-chloro-6-nitrocholest-5-en-7-one (LXII), 5,6-seco-6-nitro-5,6-diketocholest-3-ene (LXIII), and 3-chloro-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane (LXIV)</u>

To the suspension of the compound (LVIII)(5 g) in glacial

acetic acid (100 ml) was added chromium trioxide (10 g) in acetic acid and water mixture (10 ml each) as described earlier. Usual work up of reaction mixture provided a residue which was chromatographed over silica gel (100 g). Elution with light petroleum-ether (20:1) afforded 3β-chloro-6-nitrocholest-5-en-7-one (LXII), recrystallized from light petrol (1.37 g), m.p. 155°.

Analysis Found : C, 69.90; H, 9.00; N, 3.00

$C_{27}H_{42}NO_3Cl$ requires : C, 69.97; H, 9.07; N, 3.02%.

UV : λ 251 nm.

IR : $\nu_{max.}$ 1690 (C=C-C=O), 1540 and 1390 (C-NO_2), 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 3.78 (m, $W\frac{1}{2}$ = 17 Hz, C3α-H), 1.3 (C10β-CH_3), 0.68 (C13β-CH_3), 0.9 and 0.83 (other methyl protons).

Further elution with light petroleum-ether (19:1) provided 5,6-seco-6-nitro-5,6-diketocholest-3-ene (LXIII), recrystallized from light petroleum (0.80 g), m.p. 170°.

Analysis Found : C, 72.78; H, 9.60; N, 3.90

$C_{27}H_{43}NO_4$ requires : C, 72.80; H, 9.66; N, 2.88%

IR : $\nu_{max.}$ 1670-1680 (-$\overset{O}{\overset{\|}{C}}$-$NO_2$, -C=C-C=O), 1620 (C=C), 1535 and 1390 cm^{-1} (C-NO_2).

^{1}H-NMR : δ 6.9 (m, C3-H), 6.1 (d, C4-H), 1.2 (C10β-CH_3), 0.7 (C13β-CH_3), 1.0, 0.93 and 0.83 (other methyl protons).

Elution with light petroleum-ether (10:1) afforded 3-chloro-4,5:5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxy-cholestane (LXIV) as a non crystallizable oil (1.8 g).

Analysis Found : C, 63.13; H, 8.50; N, 2.70

$C_{27}H_{46}NO_6Cl$ requires : C, 63.15; H, 8.57; N, 2.72%.

IR : $\nu_{max.}$ 3500-3450 (-OH), 1690-1730 (-COOH, -CHO and $-CONO_2$), 1520 and 1370 ($-C-NO_2$), 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 10.6 (br,s, -COOH, exchangeable with D_2O), 7.3 (s, -CHO), 3.78 (m, $W\frac{1}{2}$ = 16 Hz, C3 -H), 1.3 (C10β-CH_3), 0.71 (C13β-CH_3), 1.15 and 0.9 (other methyl protons).

Reaction of the compound (LXIV) with diazomethane: Methyl 3-chloro-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitrocholestane-10-carboxylate (LXV)

An ethereal solution of LXIV (120 mg) was treated with an excess of an ethereal solution of diazomethane and was allowed to stand in the cold. Usual work up of the reaction mixture provided LXV , recrystallized from light petroleum (110 mg), m.p. 147°C.

Analysis Found : C, 65.31; H, 8.87; N, 2.53;

$C_{28}H_4NO_6Cl$ requires : C, 65.33; H, 8.89; N, 2.54%.

IR : $\nu_{max.}$ 1720-1740(HCO, CO NO_2, $COOCH_3$), 1520, 1360 ($C-NO_2$), 1240, 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 7.3 (s, CHO), 3.7 (m, C3-H), 3.6 (s, $COOCH_3$), 1.31 (C10β-CH_3), 0.70 (C13β-CH_3), 1.16 and 0.93 (other methyl protons).

Chromic acid oxidation of 3β-acetoxy-6-nitrocholest-5-ene(LIX): 3β-acetoxy-6-nitrocholest-5-en-7-one (LXVI) and 3-acetoxy-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane(LXVII)

A suspension of compound (LIX) (5 g) in glacial acetic acid (100 ml) was treated with a solution of chromium trioxide (10 g) in 20 ml of acetic acid and water mixture (1:1) as described earlier. Usual work up of the reaction mixture provided a residue which was chromatographed over silica gel (100 g). Elution with light petroleum-ether acetate (5:1) afforded 3β-acetoxy-6-nitrocholest-5-en-7-one (LXVI), recrystallized from light petrol (1.2 g), m.p. 180°.

Analysis Found : C, 71.43; H, 9.22; N, 2.85

$C_{29}H_{45}NO_5$ requires : C, 71.45; H, 9.24; N, 2.86%.

UV : λ 250 nm.

IR : $\nu_{max.}$ 1730 ($-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1680 (-C=C-C=O), 1620 (C=C), 1525 and 1370 ($C-NO_2$), 1240 and 1040 cm^{-1} (acetate).

^{1}H-NMR : δ 4.6 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H), 2.12 ($-O\overset{\overset{O}{\|}}{C}-CH_3$), 1.28 (C10β-$CH_3$), 0.65 (C13β-$CH_3$), 1.2, 0.86, and 0.80 (other methyl protons).

Further elution with light petroleum-ethyl acetate (4:1) provided 3-acetoxy-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitro-10-carboxycholestane (LXVII) as a non crystallizable oil (2.1 g).

Analysis Found : C, 66.75; H, 9.00; N, 2.66

$C_{29}H_{47}NO_8$ requires : C, 66.79; H, 9.02; N, 2.68%.

IR : $\nu_{max.}$ 3500-3400 (-OH), 1740-1690 (-$\underline{CO}NO_2$, -$C\underline{H}O$, -$O\underline{CO}CH_3$ and -$\underline{CO}OH$), 1530 and 1370 (C-NO_2), 1240 and 1040 cm^{-1} (acetate).

^{1}H-NMR : δ 10.26 (br,s, -COO$\underline{H}$, exchangeable with D_2O), 7.35 (s, -C$\underline{H}$O), 4.6 (m, $W\frac{1}{2}$ = 17 Hz, C3-$\underline{H}$), 2.0 (s, -OCOC$\underline{H}_3$), 1.23 (C10β-C$\underline{H}_3$), 0.73 (C13β-C$\underline{H}_3$), 1.16 and 0.95 (other methyl protons).

Reaction of the compound (LXVII) with diazomethane: Methyl 3-acetoxy-4,5: 5,6-bis-seco-3-formyl-6-keto-6-nitrocholestane-10-carboxylate (LXVIII)

The ethereal solution of (LXVII) (120 mg) was treated with an excess of an ethereal solution of diazomethane and was allowed to stand in the cold. Usual work up of the reaction mixture provided LXVIII, recrystallized from light petrol (100 mg), m.p. 134°.

Analysis Found : C, 65.31; H, 8.87; N, 2.53

$C_{30}H_{49}NO_8$ requires : C, 65.33; H, 8.89; N, 2.54%.

IR : $\nu_{max.}$ 1735-1725 (-$\underline{CO}OCH_3$, -$\underline{CO}NO_2$ -$O\underline{CO}CH_3$, -$C\underline{H}O$), 1520 and 1360 (C-NO_2), 1240, 1030 cm^{-1} (acetate).

^{1}H-NMR : δ 7.3 (s,-C$\underline{H}$O), 4.7 (m, $W\frac{1}{2}$ = 18 Hz, C3-$\underline{H}$), 3.7 (s, -COOC$\underline{H}_3$), 2.1 (s, -OCOC$\underline{H}_3$), 1.25 (C10β-C$\underline{H}_3$), 0.74 (C13β-C$\underline{H}_3$), 1.16 and 0.97 (other methyl protons).

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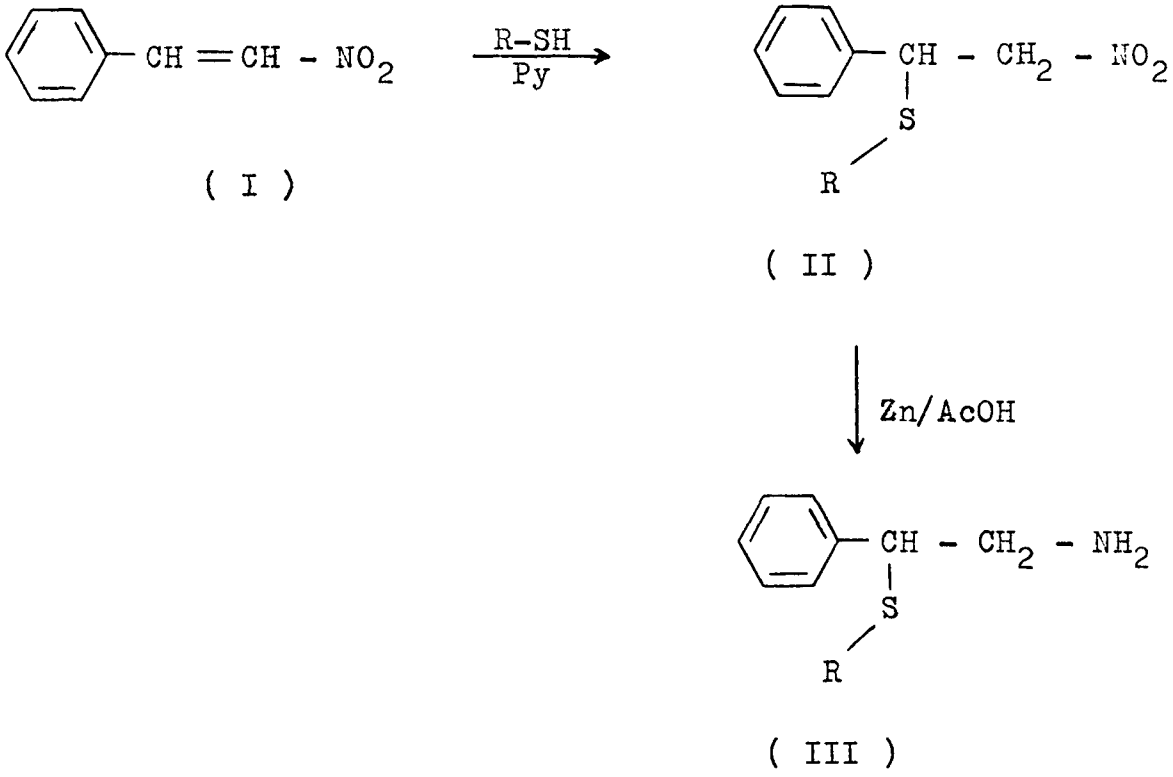
Part-Two

Reduction of Steroidal Nitro Olefins

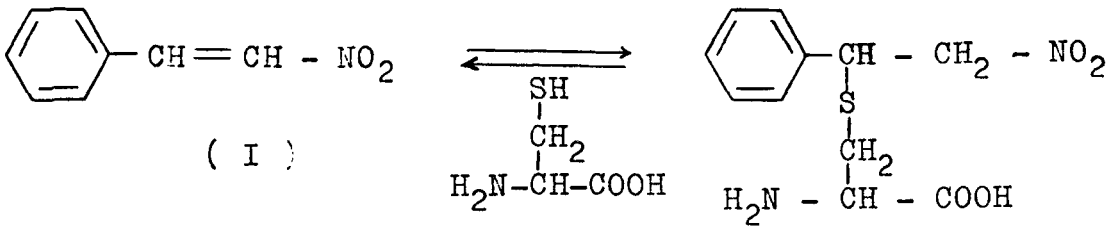
THEORETICAL

The first report of the reaction of nitro olefins with thiols came in 1958 when Drain and Macrae[1] carried out the Michael addition of certain thiols to β-nitrostyrene (I). The resulting nitrothioether (II) when reduced with zinc acetic acid gave the amino derivative (III) which was found useful for the treatment of rheumatoid arthritis and other inflammations.



(I) (II) (III)

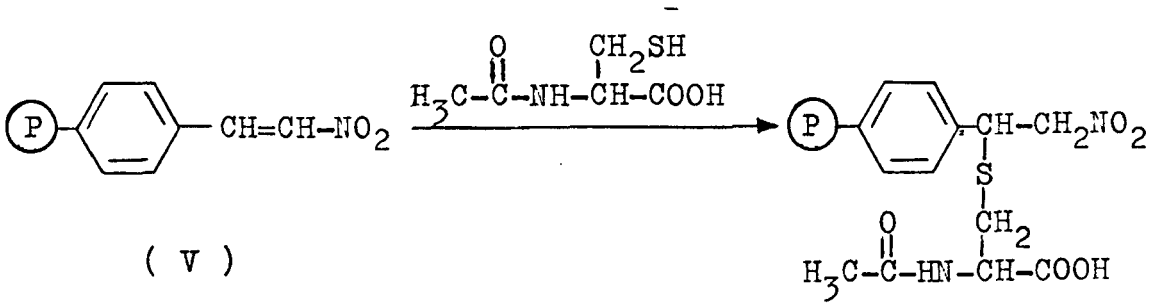
A similar type of addition has also been reported by Jung et al.[2] when β-nitrostyrene was treated with cysteine.



(I)

(IV)

Heusel and Jung[3] reported the reaction of polymer bound β-nitrostyrene (V) which yielded the same type of addition product with cysteine peptide.

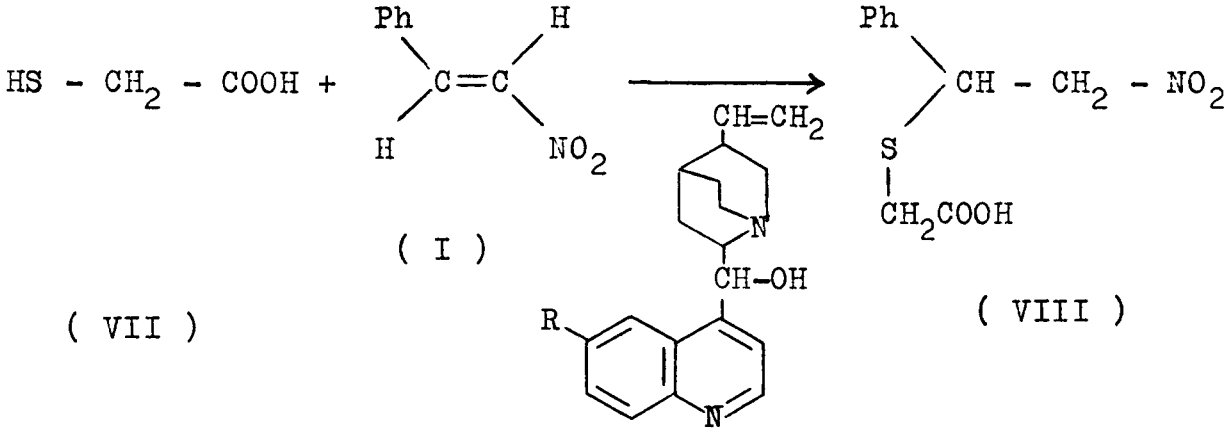


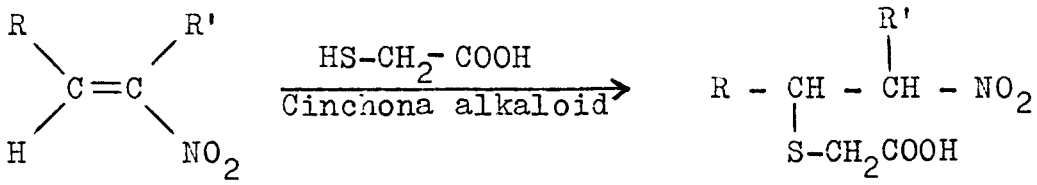
(V)

(VI)

Recently, Kobayashi and Iwai[4] have investigated the addition of thioglycolic acid (VII) to nitrostyrene (I) under

the influence of Cinchona alkaloid, especially quinine in 58% yield. Similar asymmetric addition of thioglycolic acid to other nitro olefins was also studied.

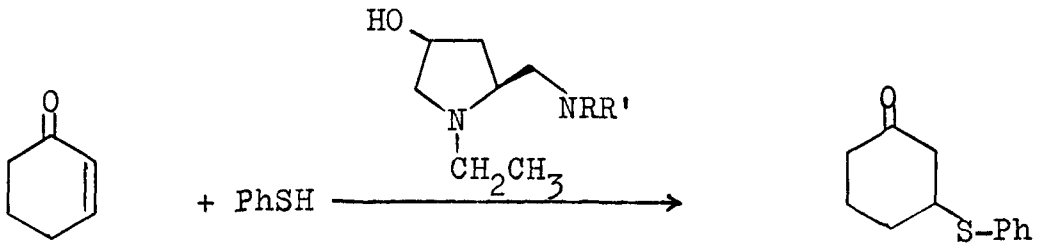




	R	R'		R	R'
(IX)	$2\text{-}CH_3OC_6H_4$	H	(XII)	$2\text{-}CH_3OC_6H_4$	H
(X)	C_6H_5	CH_3	(XIII)	C_6H_5	CH_3
(XI)	$CH_3OCO(CH_2)_4$	H	(XIV)	$CH_3OCO(CH_2)_4$	H

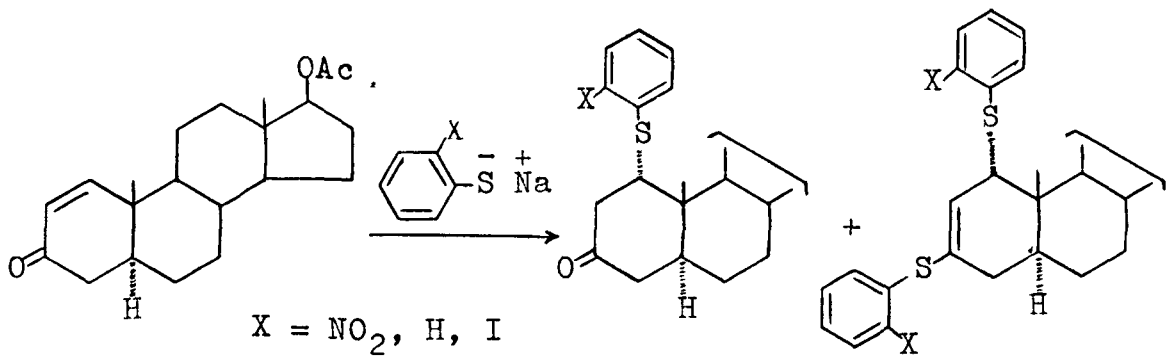
Mukaiyama et al.[5] carried out the asymmetric addition of thiols to 2-cycloalkenone using chiral aminoalcohols, derived from L-hydroxyproline or (S)-proline as base catalysts. The reaction of phenylmercaptan with 2-cyclohexen-1-one in toluene

at -5°C using the catalyst (2S, 4S)2-anilinomethyl-1-ethyl-hydroxypyrrolidine gave 3-phenylthio-1-cyclohexanone (XVI), in good optical yields (47-88%).



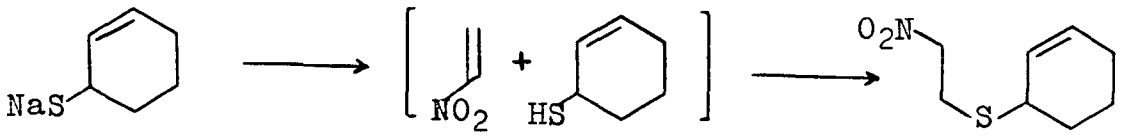
(XV) (XVI)

Michael addition at C1 of 17-acetoxy-5α-androst-1-en-3-one (XVII) was investigated by Campbell et al.[6] Acid catalysed reaction of XVII with excess of phenyl mercaptan derivatives gave adducts (XVIII) and (XIX).



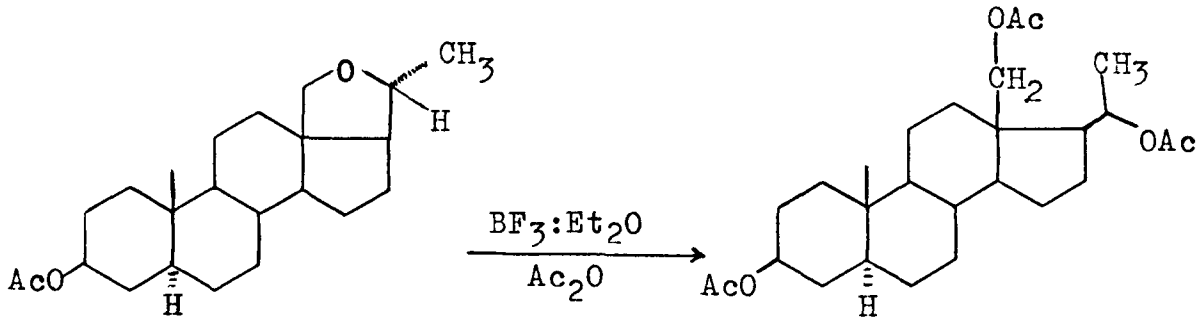
(XVII) (XVIII) (XIX)

Confalone et al.[7] generated, in situ, mercaptide (XXI) by treating one equiv. of 1-nitro-2-acetoxyethane with XX which presumably generated nitroethylene and the mercaptan (XX-a). These intermediates then underwent Michael addition to give (XXI).



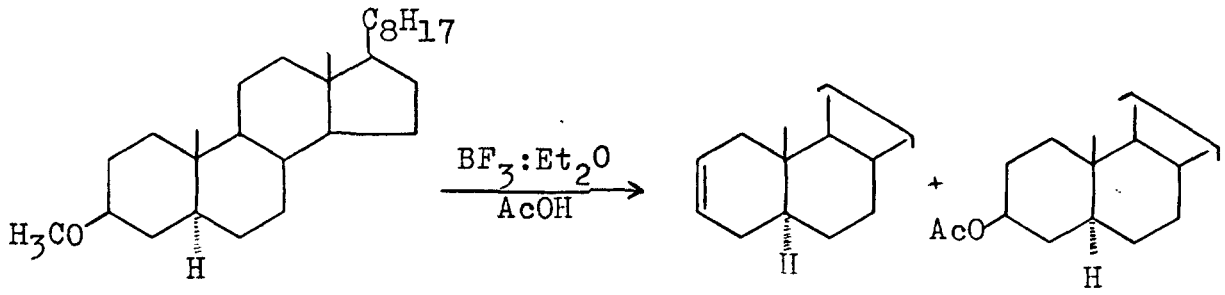
(XX) + $O_2N-CH_2-CH_2OAc$ (XX-a) (XXI)

Kamber et al.[8] used boron-trifluoride and acetic anhydride at room temperature to cleave steroid 18,20-epoxide (XXII) to the 18,20-diacetate (XXIII). Cleavage of cholesteryl methylether in BF_3:AC_2O mixture at 0°C gave 93% yield of cholesteryl acetate[9].



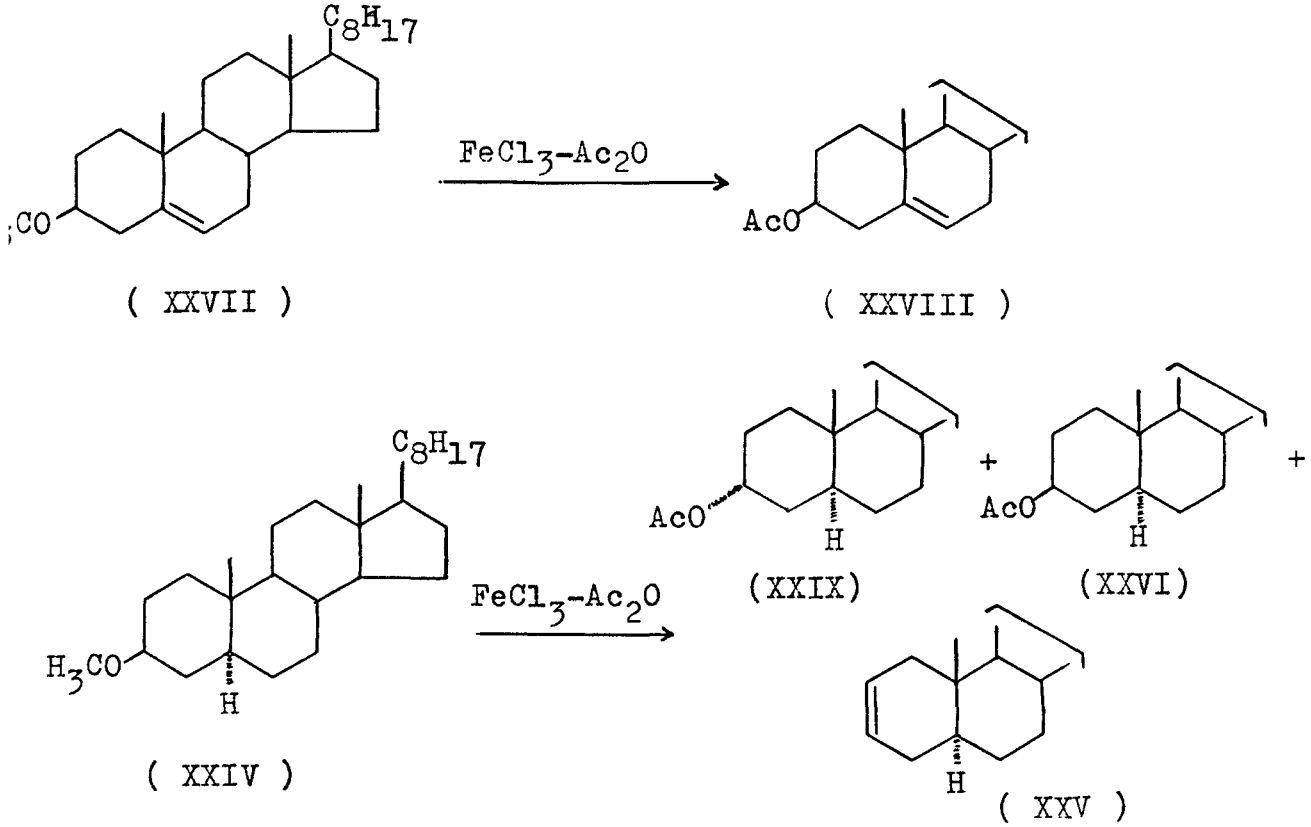
(XXII) (XXIII)

Youssefyeh and Mazur[10] carried out the cleavage of 3β-methoxycholestane (XXIV) with BF_3-etherate and acetic acid to cholest-2-ene (XXV) and 3β-acetoxycholestane (XXVI) in 80-85% yield. Lithium halide was essential for such cleavage.

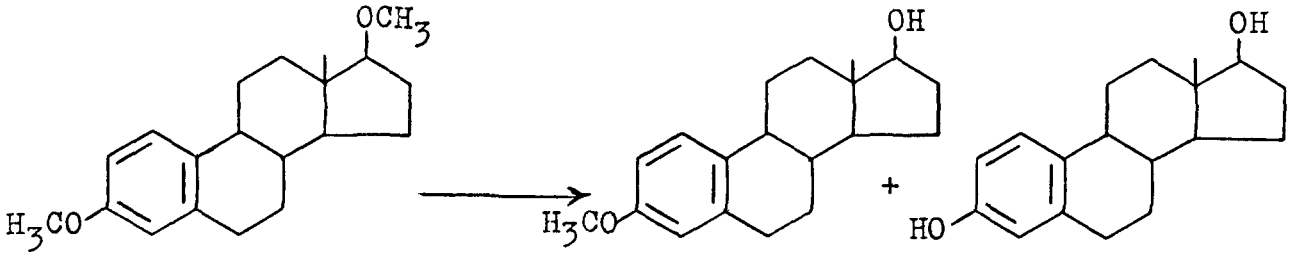


(XXIV) (XXV) (XXVI)

Ganem and Small, Jr.[11] suggested that cholesteryl methylether (XXVII) can be smoothly transformed to cholesteryl acetate (XXVIII) in high yield and cholestanyl methylether (XXIV) can be converted to a mixture of 3α- and 3β-cholestanyl acetates (XXIX) and (XXVI) respectively as well as to Δ^2-cholestene (XXV) by exposing methylethers to a trace of ferric chloride in acetic anhydride as solvent ($FeCl_3$-Ac_2O).

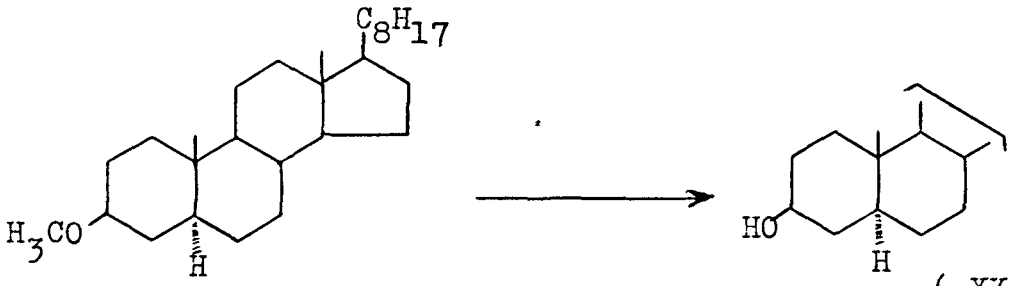


Demethylation of aliphatic methylether with a thiol and boron trifluoride was reported by Fujita et al.[12]. It was proposed that treatment of primary and secondary alkyl methylethers with BF_3-ether complex in several thiols gave the corresponding alcohols in good yields. In case of secondary alkyl methylether (XXX), the alcohols (XXXI) and (XXXII) were formed with retention of the original stereochemistry. This work was therefore used for total synthesis of Gibberellins A_{15} and A_{37}[13].

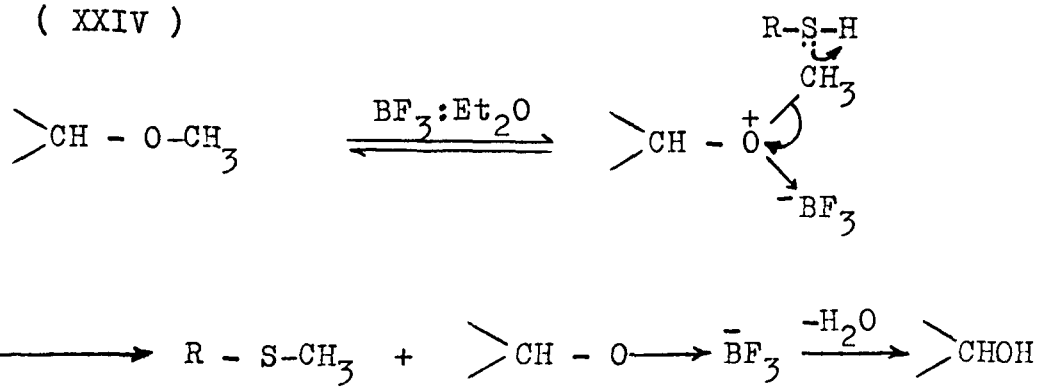


(XXX) (XXXI) (XXXII)

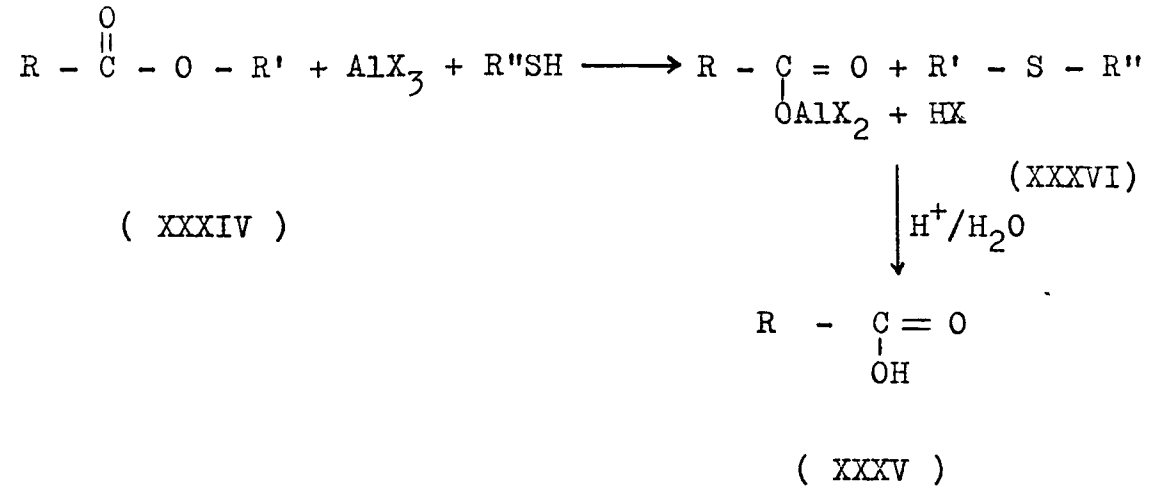
Cholestanyl methylether (XXIV) was converted to cholestanol (XXXIII) in 70-80% yield[12]. The role of thiol in the ether cleavage was explained as follows:



(XXIV) (XXIII)

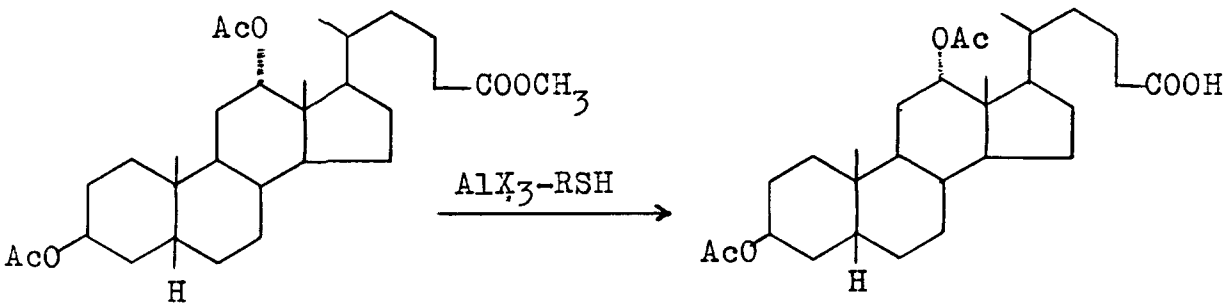


The aluminium halide-thiol system was proved to be very effective demethylation agent for aliphatic as well as aromatic methylethers and its application was extended to demethylation of methylenedioxy compounds by Fujita et al.[14]



(XXXIV)

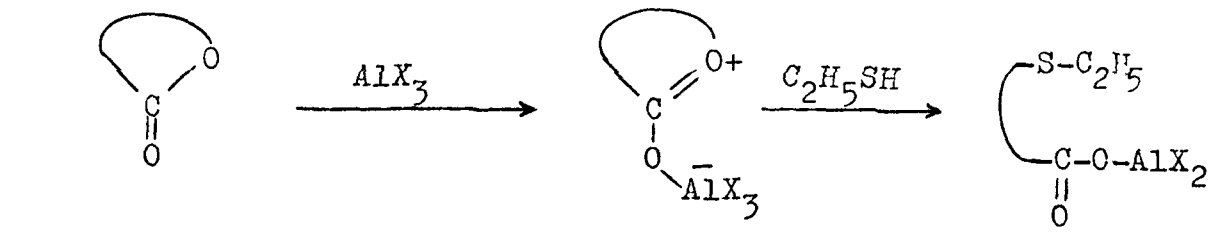
(XXXV)



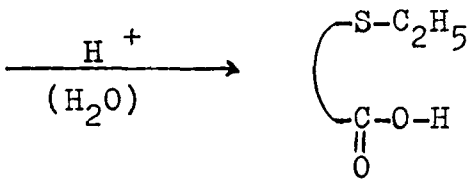
(XXXVII)

(XXXVIII)

Subsequently, aluminium halide-thiol system was applied to lactone (XXXIX). The reaction proceeded as shown below and gave ω-ethylthio-carboxylic acid (XL) in good yield.

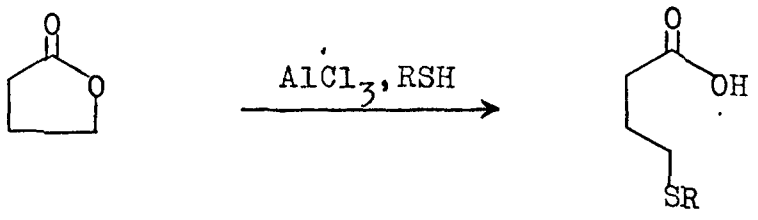


(XXXIX)



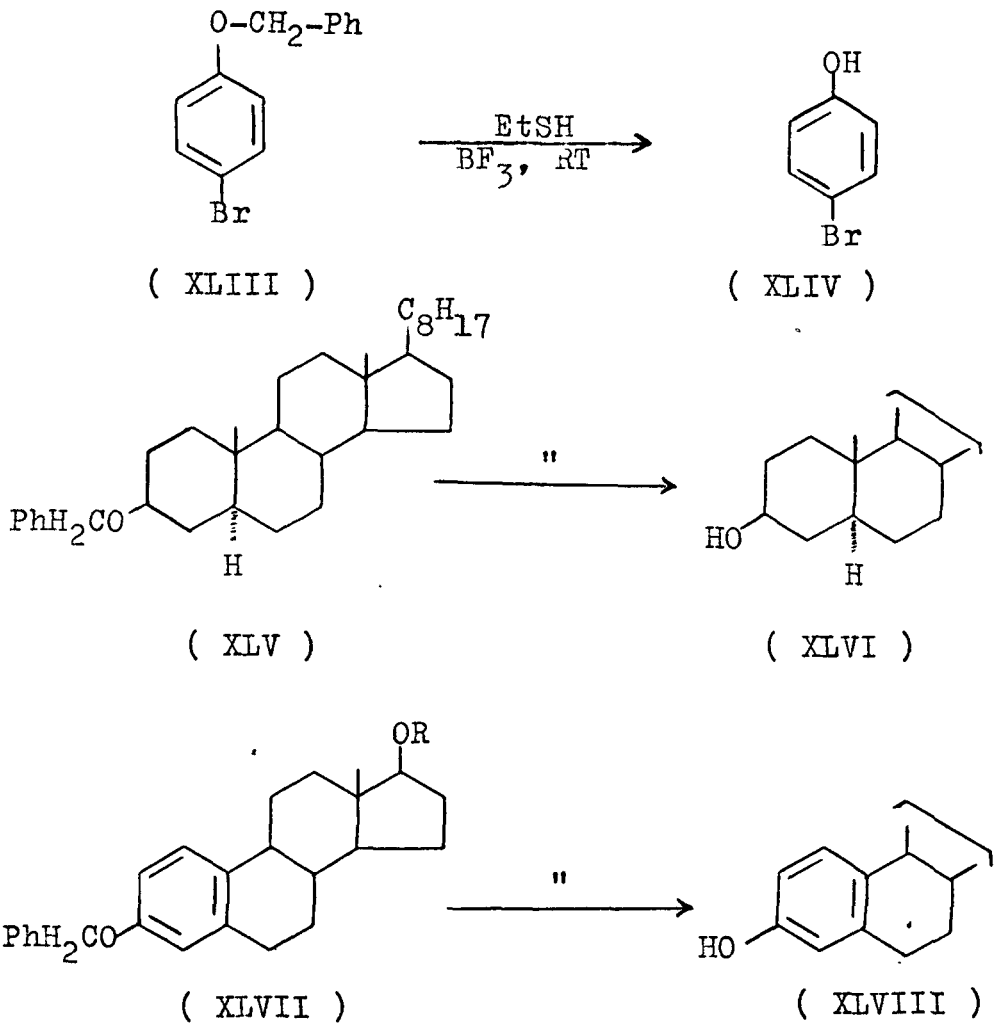
(XL)

Fujita et al.[15] converted lactone (XLI) to thiocarboxylic acid (XLII) in high yield when it was treated with $AlCl_3$ and alkanethiol.

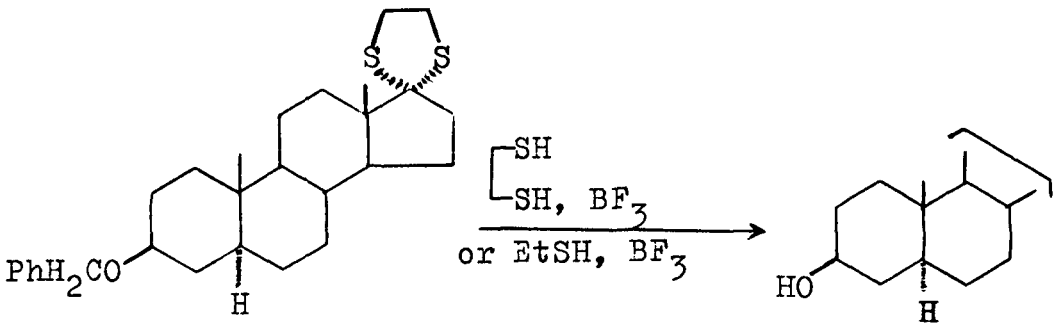


(XLI) (XLII)

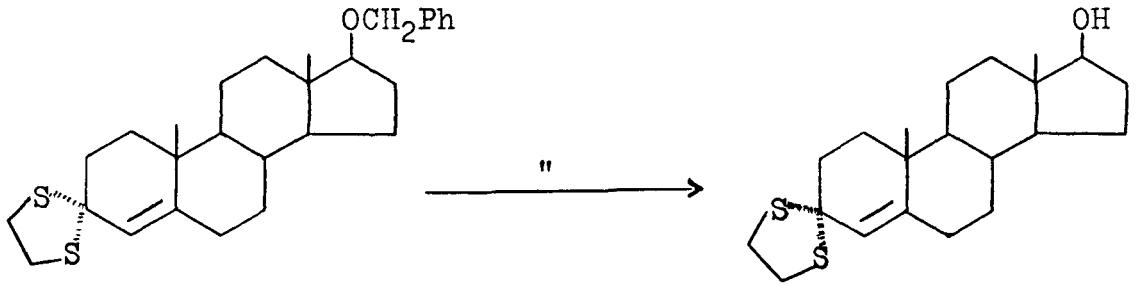
The removal of benzyl protecting group of phenols with boron trifluoride-etherate in EtSH at room temperature in methylene dichloride was studied by Fujita et al.[16]



Dithioacetals (XLIX) and (LI) were converted to corresponding alcohols (L) and (LII) respectively, also in high yield without touching dithioacetal moiety by using ethanedithiol or ethanethiol[16].

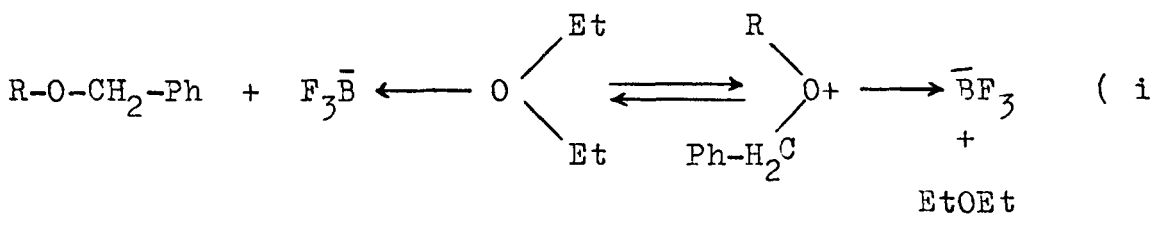


(XLIX) (L)

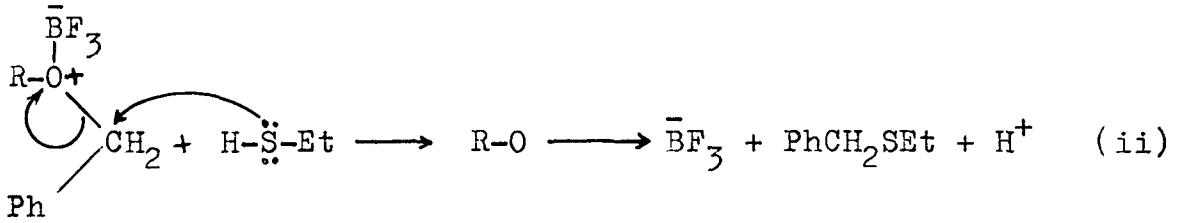


(LI) (LII)

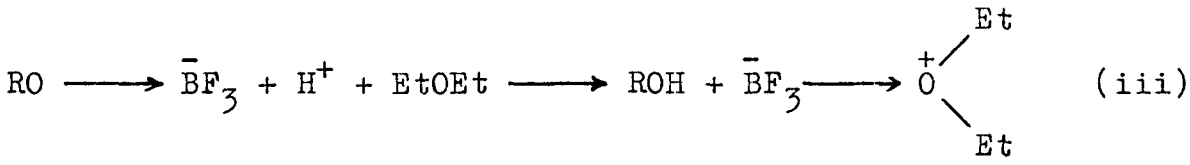
It was also observed that the rate of reaction depends upon the concentration of BF_3:Et_2O. The possible mechanism of debenzylation was given as follows[16].



(i)



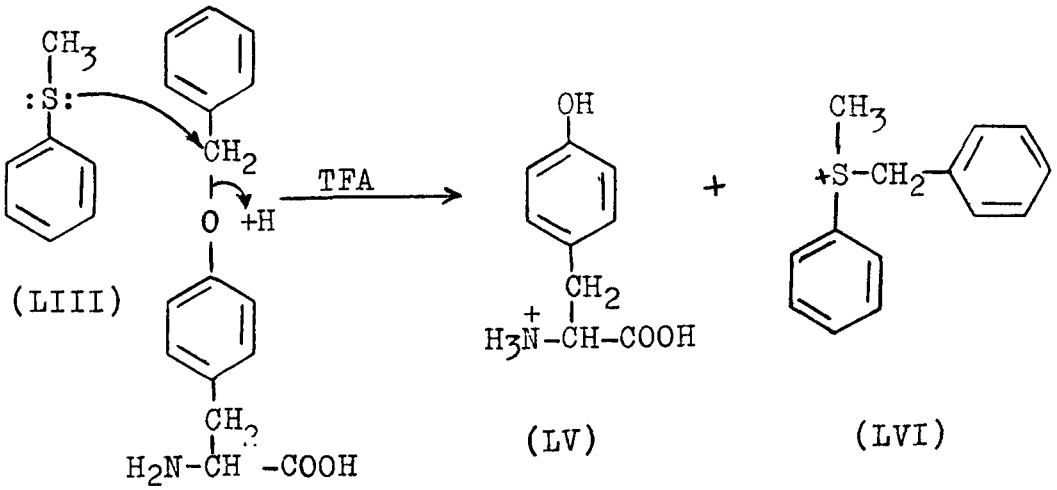
(ii)



(iii)

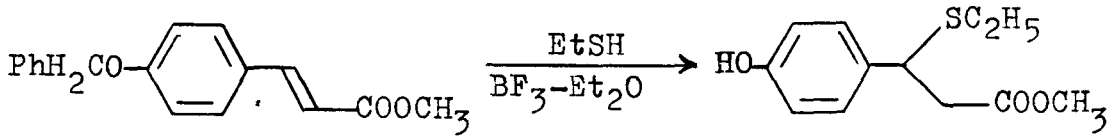
The benzylether oxygen coordinates to BF_3 to form an oxonium species (i), then a soft nucleophile, thiol attacks the soft benzyl carbon atom in an SN^2 manner to complete the cleavage of benzylether. Cleavage of the C-O bond with the BF_3 and thiol system is based on the balance between the coordination of a hard acid with the oxygen atom in benzyl ether (pulling factor) and the nucleophilic attack of the soft nucleophile to the carbon atom (pushing factor).

Another system of reagents (thioanisole and trifluoroacetic acid) for the cleavage of C-O bond in benzylethers has been reported by Kisho et al.[17] Benzyl group attached at the phenolic oxygen of tyrosine (LIV) can be quantitatively cleaved by push-pull mechanism using the thioanisole-trifluoroacetic acid (TFA) system without any side reaction.

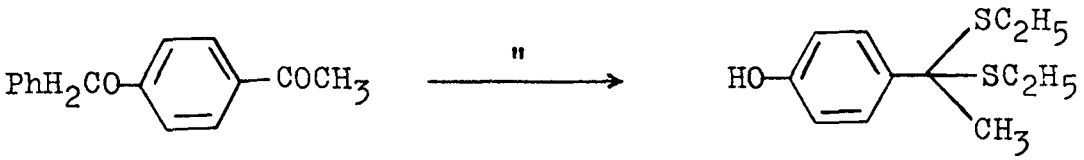


(LIII) (LIV) (LV) (LVI)

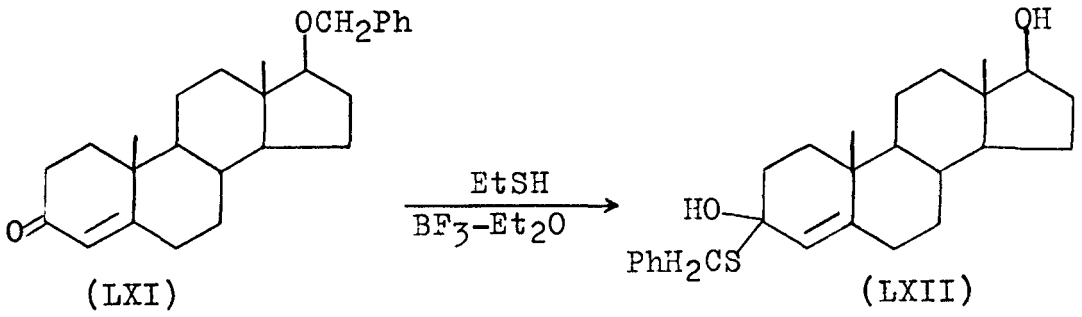
Fujita et al.[18] proposed that the benzylether (LVII) afforded debenzylated Michael adduct (LVIII) with boron trifluoride etherate-ethanethiol. Similar treatment of LIX and LXI gave unstable products LX and LXII in 89% yield.



(LVII) (LVIII)

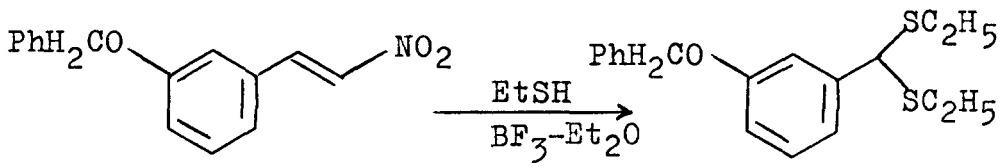


(LIX) (LX)



(LXI) (LXII)

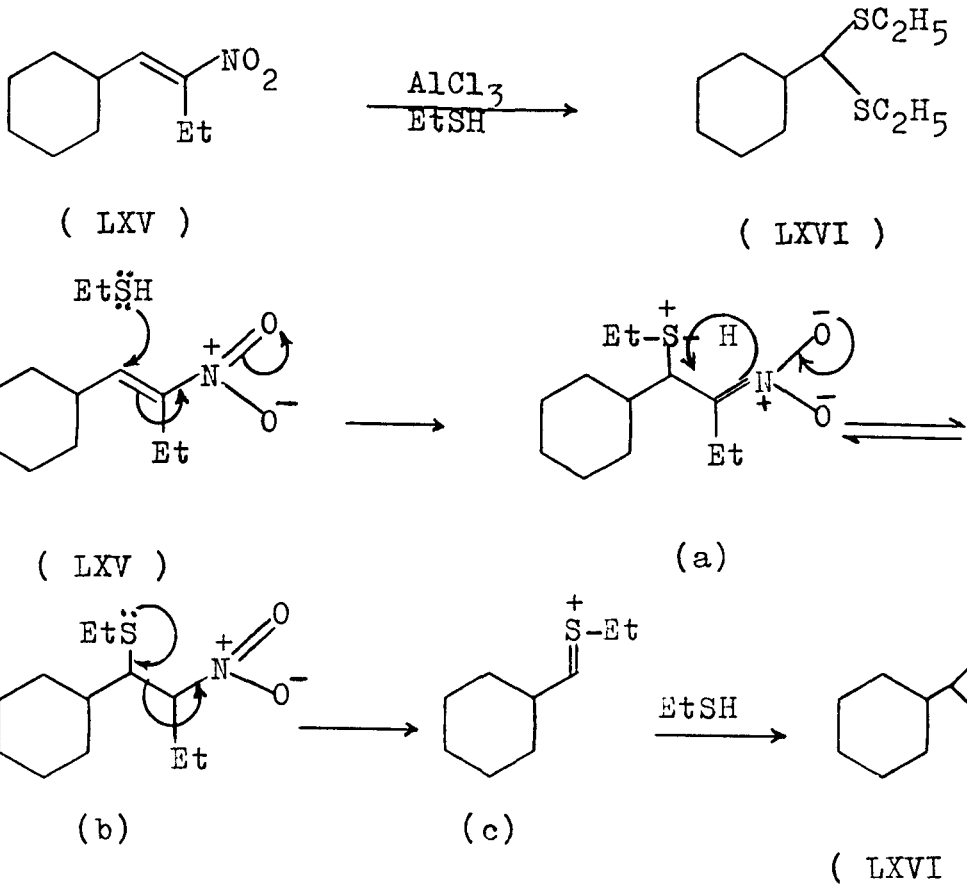
Unexpected cleavage of carbon-carbon double bond of the α,β-unsaturated nitro compound (LXIII) was observed instead of Michael addition with BF_3:Et_2O-ethanethiol in 47.7% yield[18].



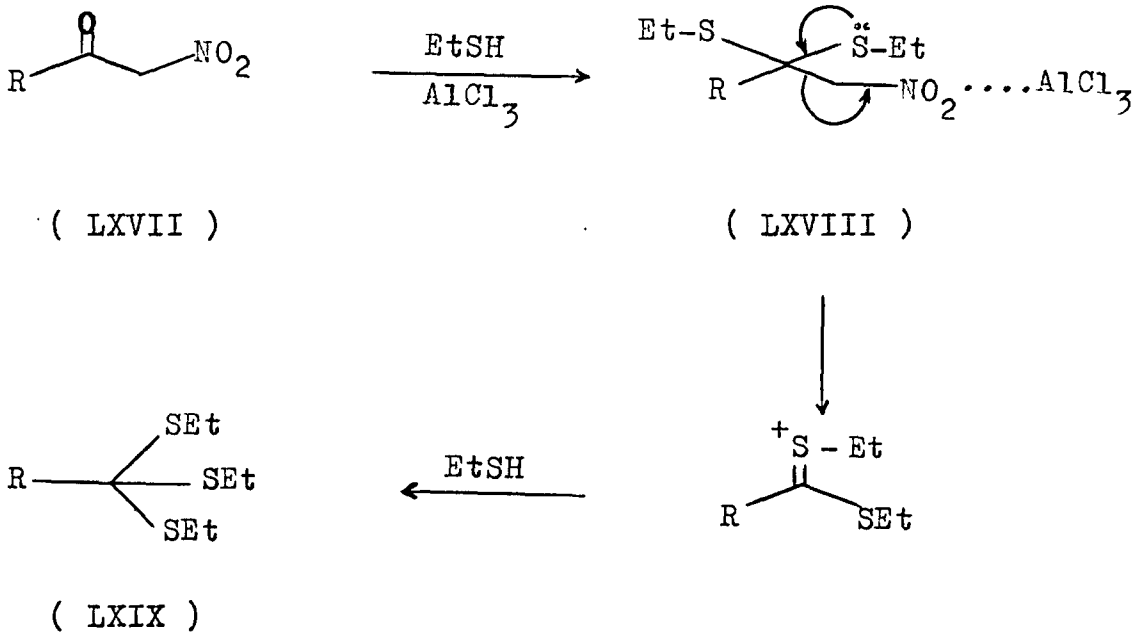
(LXIII) (LXIV)

Later Fujita et al.[19] proposed that all these carbon-oxygen bond cleavage reactions have been accomplished by changing the balance between the pulling factor (the coordination of hard acid with oxygen atom) and the pushing factor (the nucleophilic attack of soft nucleophile to the carbon atom). The order of the activity of metal halides ($ZnCl_2$ < $FeCl_3$ < $AlCl_3$ < $AlBr_3$) corresponds to that of the reported hardness[20] of them. The fact that the reaction ceases at the stage of Michael addition or proceeds further to cleave the

carbon-carbon bond depends upon the pKa-value of the leaving active methylene group. Those compounds which have the leaving group of smaller pKa-value than diethyl malonate (approx. pKa in water is 14) can be cleaved with this system of reagents.



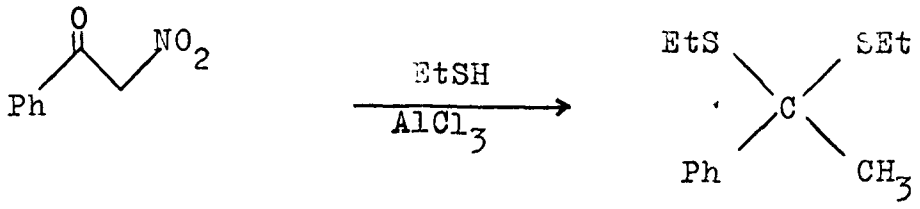
Fujita et al.[21] expected similar cleavage of bonds on treatment of α-nitroketones with combination system of reagents if the same type of mechanism is operative under similar reaction conditions.



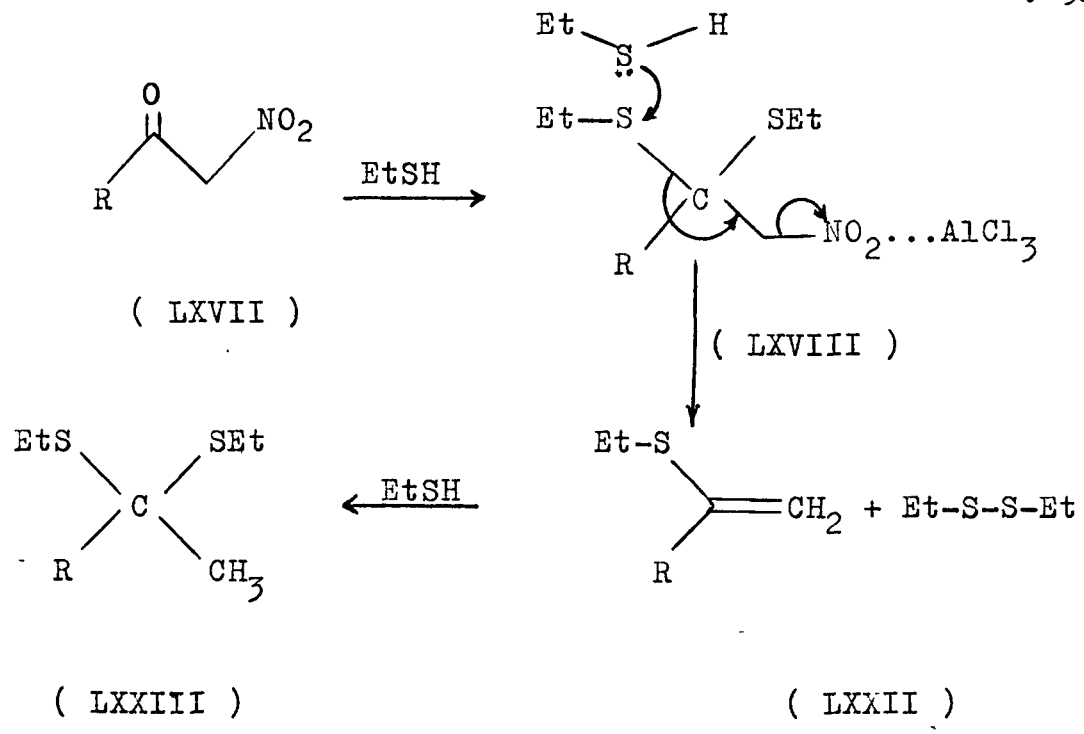
(LXVII) (LXVIII)

(LXIX)

Unexpectedly, however, the attempted reaction of LXX with $AlCl_3$ and ethanethiol afforded a 78% yield of dithioacetal (LXXI) where nitro group was replaced by hydrogen atom. This was the first report on the reductive displacement of the nitro group to the hydrogen atom in acedic media[21].



(LXX) (LXXI)



Different modes of reaction can be attributed to the polarizability of the carbon sulphur bond[21]. Deslongchamps et al.[22] have shown that in the most stable conformation of dithioacetals, one of the lone pair orbitals on each sulphur atom should be oriented antiperiplaner to another carbon-sulphur bond. Application of this principle to dithioacetal (LXVIII) leads to the conformation shown in Figure-1 as most plausible one. Thus, a carbon-sulphur bond of LXVIII is more susceptible to the attack of the ethanethiol than that of LXVa, because of the stereoelectronic assistance of the lone pair orbitals of the adjacent sulphur atom.

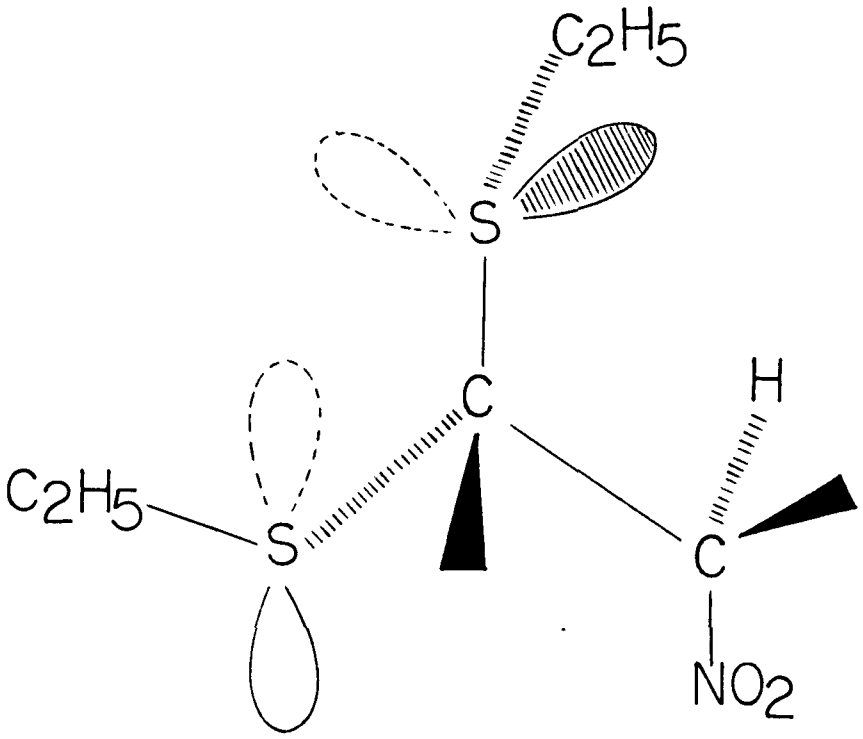
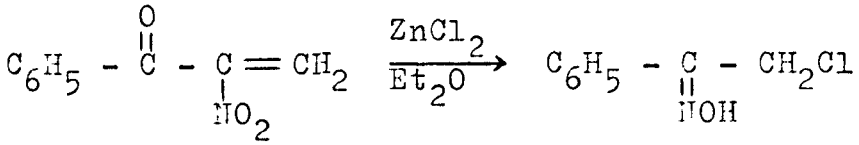
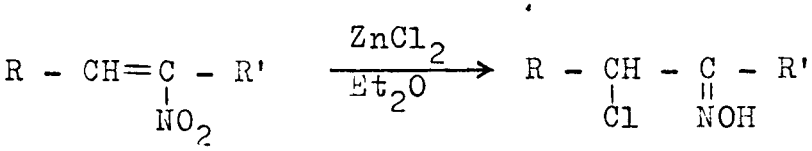


Fig. 1

Attempts have been made to convert nitro olefins directly into oximes. Dornow et al.[23] converted various nitro olefins to α-chloro oximes by reduction with zinc (II) chloride in ether.



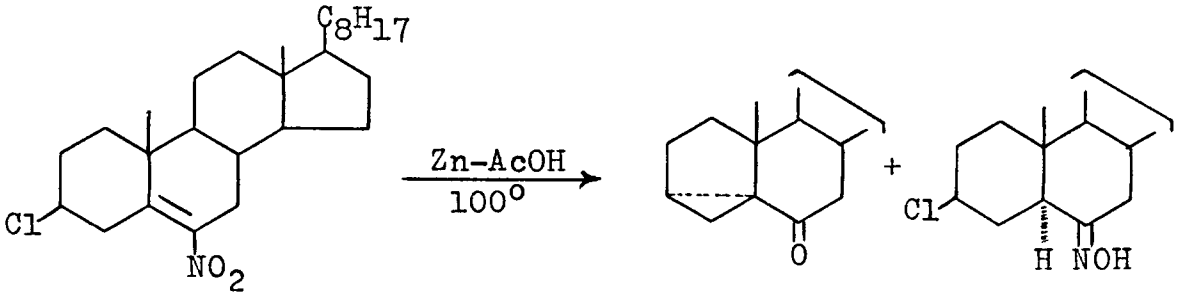
(LXXIV) (LXXV)



(LXXVI) (LXXVII)

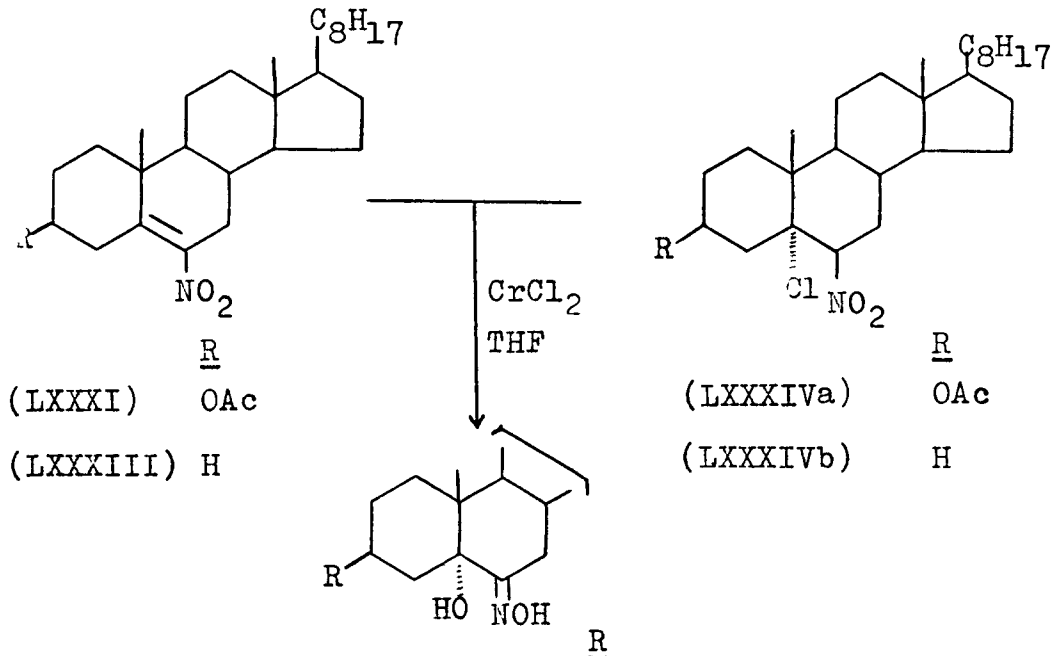
	R	R'		R	R'
a)	CH_3	CH_3	a)	CH_3	CH_3
b)	H	C_2H_5	b)	H	C_2H_5
c)	$CH_3(CH_2)_2$	C_2H_5	c)	$CH_3(CH_2)_2$	C_2H_5
d)	C_6H_5	CH_3	d)	C_6H_5	CH_3

Kaye et al.[24] treated 3β-chloro-6-nitrocholest-5-ene (LXXVIII) with zinc and acetic acid at 100° to produce 43% of 3α,5-cyclo-5α-cholestan-6-one (LXXIX) and 20% 3β-chloro-5α-cholestan-6-one oxime (LXXX).



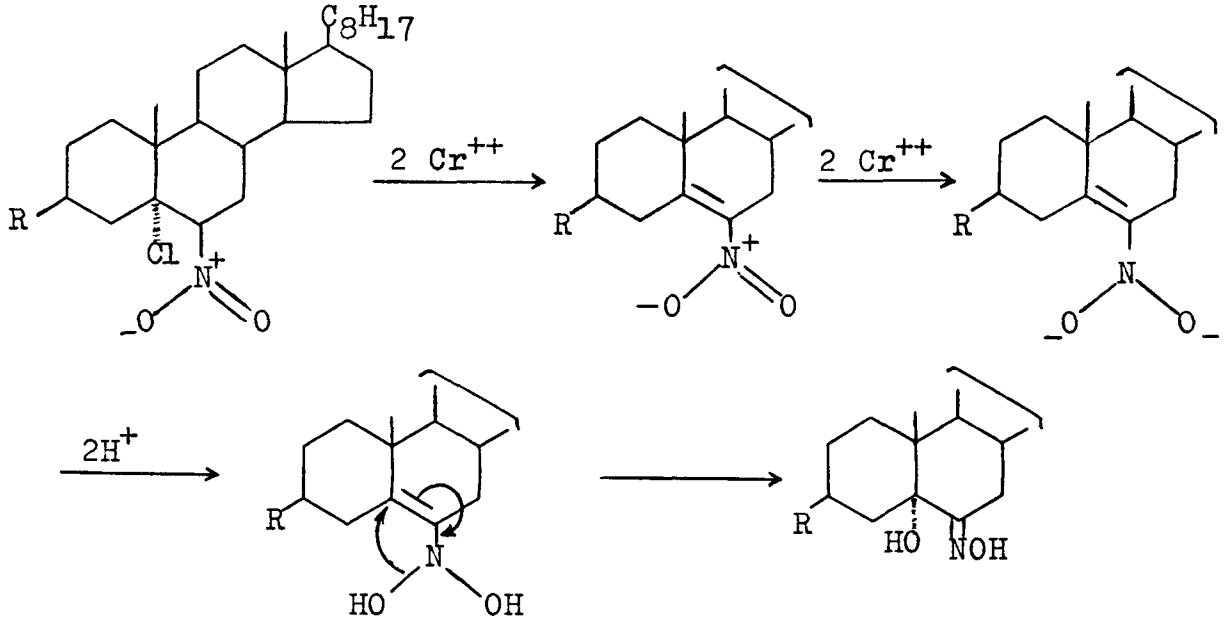
(LXXVIII) (LXXIX) (LXXX)

Hanson and Premuzic[25] have reported the reduction of 6-nitrocholesteryl acetate (LXXXI) with 0.1M chromous chloride in refluxing tetrahydrofuran to give the oxime of 3β-acetoxy-5α-hydroxycholestan-6-one (LXXXIIa) in 80% yield. 3β-Acetoxy-5-chloro-6β-nitro-5α-cholestane (LXXXIVa) gave the same hydroxyoxime (LXXXIIa) under identical reaction conditions.

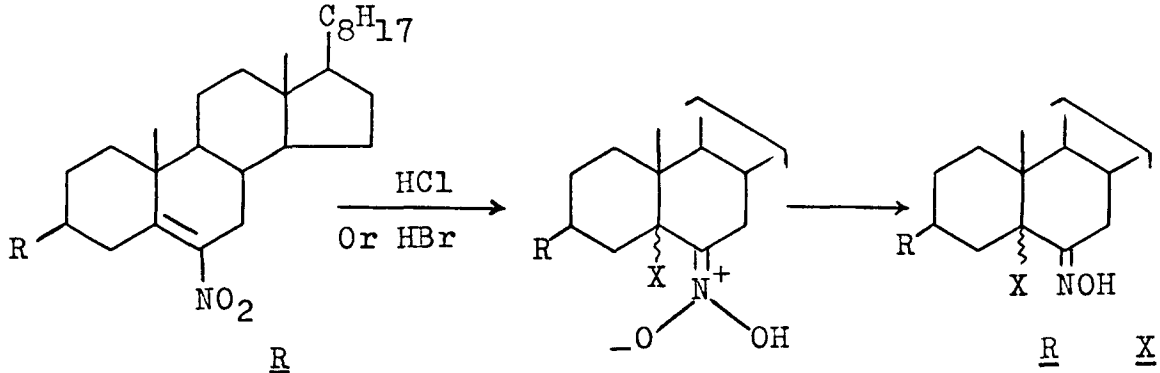


It was proposed that the first stage of the reduction of LXXXIVa to LXXXIIa involves the reductive elimination of HCl. Hence by analogy with the reduction of bromohydrins[26], addition of a hydrogen donor such as butan-1-thiol might alter the course of the reaction. However, addition of excess of butan-1-thiol to the reaction of 5α-chloro-6β-nitrocholestan-3β-ol completely inhibited reduction. The same results were obtained with 3β, 5α-dichloro-6β-nitrocholestane and 6-nitrocholesteryl acetate. In the presence of a small amount of butan-1-thiol and large excess of chromous chloride the 5α-hydroxy-6-oxime was formed as the sole product [25].

The mechanism of reduction was given as shown below:



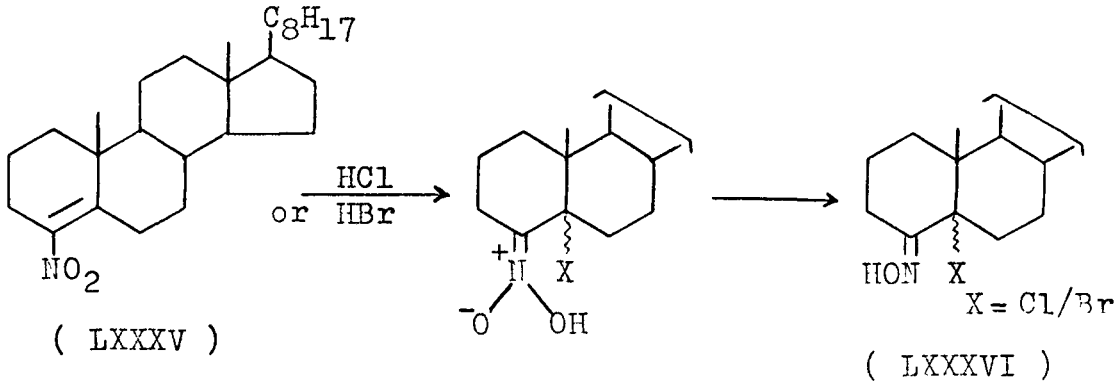
Reaction of 6-nitrocholest-5-ene with one mole of hydrogen chloride or bromide to give 5α-halo-6-oxime (LXXXIV) has been reported by Komeichi et al.[27] Similarly 4-nitrocholest-4-ene (LXXXV) gave 5α-halo-4-oxime (LXXXVI).



	R
(LXXXI)	OAc
(LXXVIII)	Cl
(LXXXIII)	H

β-Halonitronic acid Intermediate

	R	X
(LXXXIV)a	OAc	Cl/B:
b	Cl	Cl/B
c	H	Cl/B

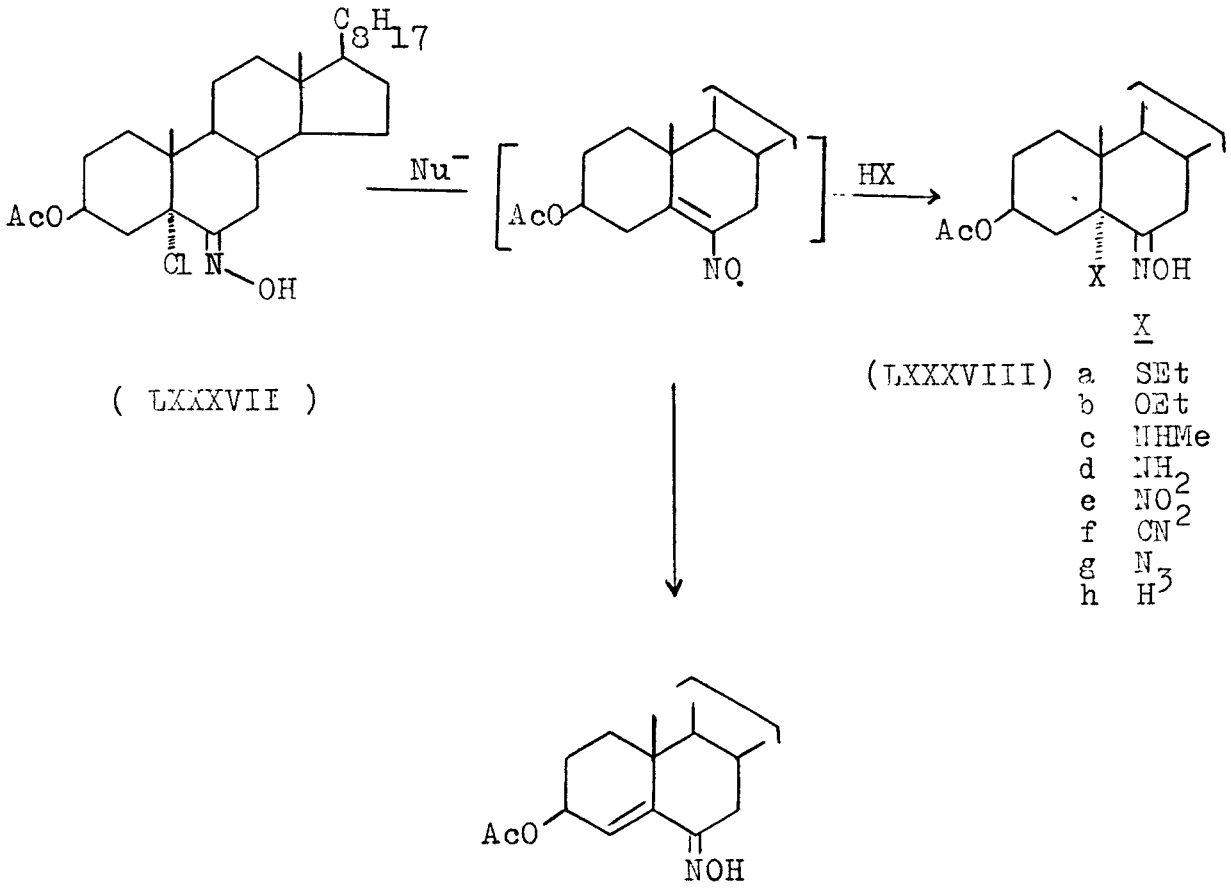


(LXXXV) (LXXXVI)

The first step of hydrogen chloride or bromide addition to the unsaturated nitrosteroids was considered to give β-halonitronic acid intermediate resulting from 1,4-addition in ordinary way. It was proposed that the initially formed β-halonitronic acid intermediate failed to react with more reagent, and stabilized with loss of oxygen atom to give α-halooxime. To account for this difference, it was postulated that the steric hindrance towards C=N of the intermediate is exerted by the axial halogen, and less effectively, by angular methyl groups, both being two atoms removed from nitrogen and carbon of the C=N grouping respectively[27].

5α-Chlorine or bromine can be replaced smoothly with various organic and inorganic nucleophiles to afford high yield of 5α-substituted 6-oximes under mild reaction conditions. Reaction of α-chloro oximes with nucleophiles

has received considerable attention[28-32]. Pritzkow et al.[28] have shown that the reaction follows an elimination-addition mechanism. Komeichi et al.[33] treated 3β-acetoxy-5-chloro-6-hydroxyimino-5α-cholestane (LXXXVII) with various nucleophiles in dichloromethane to obtain 5α-substituted oximes (LXXXVIII).



(LXXXVII)

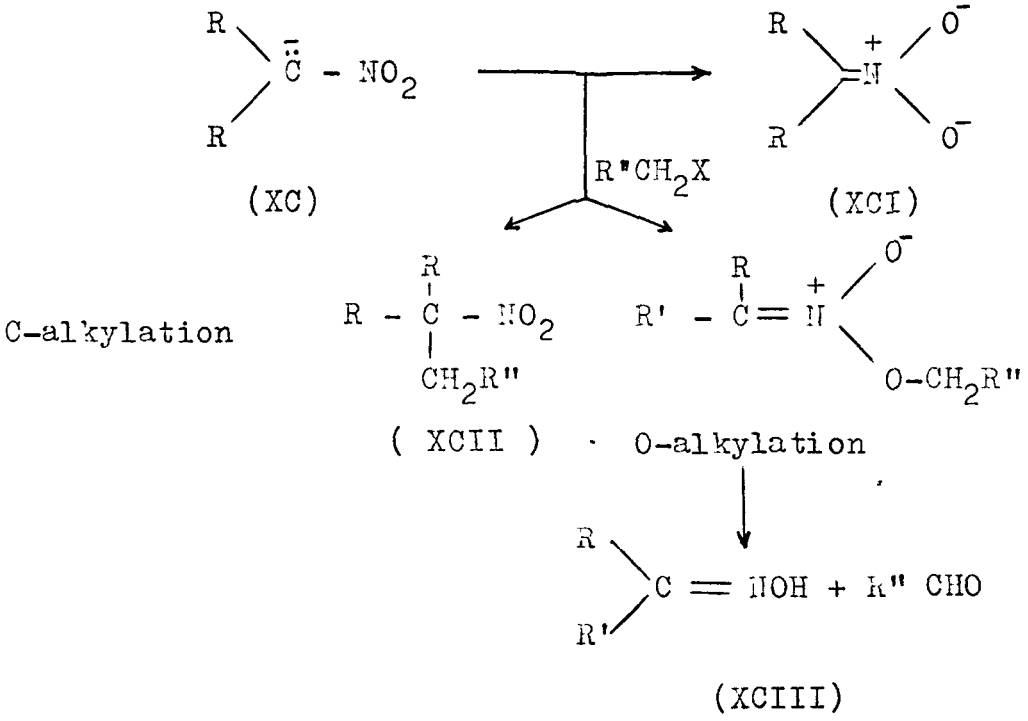
(LXXXVIII)

	X
a	SEt
b	OEt
c	NHMe
d	NH_2
e	NO_2
f	CN_2
g	N_3
h	H

(LXXXIX)

The alkylation of nitroalkane monoanions with alkyl halides may occur on either oxygen or carbon, depending upon the nature of the alkyl halide and reaction conditions[34].

O-Alkylation is more usual and gives the carbonyl compound derived from the alkyl halide and the oxime derived from nitroalkane. In 1966, Kornblum[35] and Russell[36] and their respective coworkers disclosed that the C-alkylation proceeds by a chain process involving radical anions and free radicals[37] as illustrated below for the typical reaction of the sodium salt of 2-nitropropane with p-and o-nitrobenzyl chlorides.

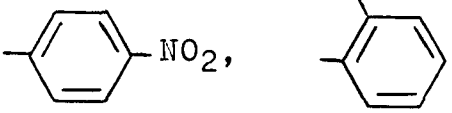


$$ArCH_2Cl + [(CH_3)_2CNO_2]^- \longrightarrow [ArCH_2Cl]^{\cdot-} + (CH_3)_2\dot{C}-NO_2$$

$$[ArCH_2Cl]^{\cdot-} \longrightarrow Ar\dot{C}H_2 + Cl^-$$

$$Ar\dot{C}H_2 + [(CH_3)_2CNO_2]^- \longrightarrow [ArCH_2-\overset{CH_3}{\underset{CH_3}{C}}-NO_2]^{\cdot-}$$

$$[ArCH_2-\overset{CH_3}{\underset{CH_3}{C}}-NO_2]^{\cdot-} + ArCH_2Cl \longrightarrow ArCH_2-\overset{CH_3}{\underset{CH_3}{C}}-NO_2 + [ArCH_2Cl]^{\cdot-}$$

Ar =  ,

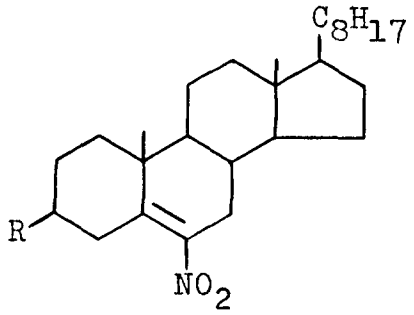
DISCUSSION

α-Nitro olefins are versatile and unique synthetic intermediates for the introduction of nucleophile or electrophile at the β- and α-carbon atoms, respectively, and for annelation reactions[38]. Further more the nitro group is convertible into such a function as an amino or a carbonyl group.

Asymmetric addition of thiols to α,β-unsaturated compounds is a reaction that possesses a potential applicability to the syntheses of physiologically active substances having a chiral centre at the α- or β-position of the sulphur atom and a topic of current interest[39,40].

A survey of the literature revealed that nitro olefins undergo Michael addition reaction on treatment with thiols, resulting in the formation of nitrothioethers[17]. In some cases the nitro olefins undergo Michael addition which is followed by the cleavage of the carbon-carbon bond with subsequent attack of another molecule of the thiol to give dithioethers[18-21]. These observations prompted us to carry out these reactions on some of the easily accessible steroidal nitro olefins. The nitro olefins selected for the present

studies are 6-nitrocholest-5-ene (LXXXIII), 3β-chloro-6-nitrocholest-5-ene (LXXVIII) and 3β-acetoxy-6-nitrocholest-5-ene (LXXXI).



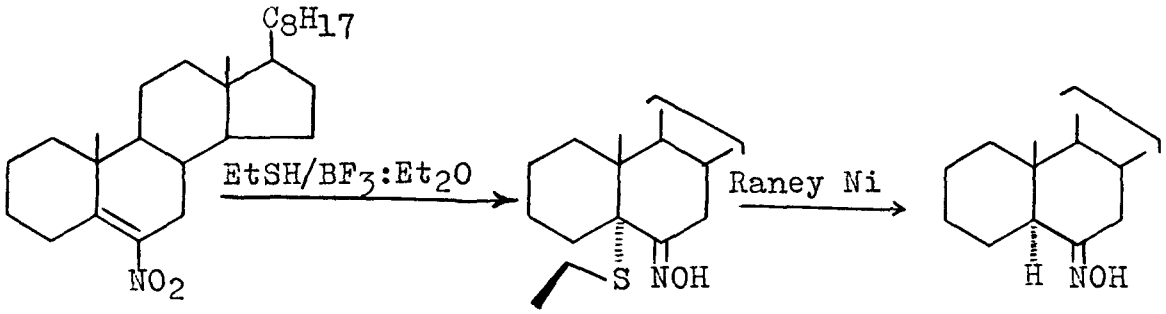
	R
(LXXXIII)	H
(LXXVIII)	Cl
(LXXXI)	OAc

Contrary to our expectations, none of the above nitro olefins resulted in the formation of either the nitrothioethers or dithioethers. They rather underwent Michael addition followed by the reaction of the nitro group under the reaction conditions to give α-oximinothioethers.

A. Reaction of 6-nitrocholest-5-ene (LXXXIII) with ethanethiol

6-Nitrocholest-5-ene (LXXXIII) was treated with ethane--thiol in dichloromethane using BF_3-etherate as a catalyst for 72 hrs at room temperature. After the completion of

reaction, the reaction mixture was worked up in the usual manner. Evoporation of the solvents and crystallization of the residue obtained, afforded a compound, m.p. 172°.



(LXXXIII) (XCIV) (XCV)

Characterization of the compound, m.p. 172° as 5-ethylmercato-5α-cholestan-6-one oxime (XCIV)

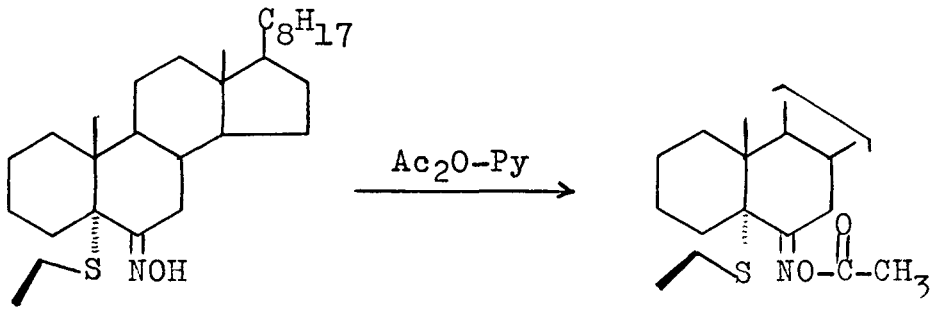
The mass spectrum of the compound (XCIV) m.p. 172° showed a molecular ion peak at m/z 461. The compound gave positive sodium nitroprusside test for sulphur, and was analysed correctly for $C_{29}H_{51}NOS$. The IR spectrum of the compound exhibited bands at 3300-3100 cm^{-1} for -OH absorption. Another absorption band at 1640 cm^{-1} was due to the C=N of the oxime group. C-S absorbed at 1440 (def.) and 1240 cm^{-1} (wag.). The NMR spectrum of the compound gave conclusive

support in favour of the structure (XCIV). It exhibited a broad singlet at δ 9.7 for hydroxy proton which disappeared on D_2O shake and a multiplet at δ 3.06 for two C7 protons, (α to =NOH). Another multiplet was displayed at δ 2.2 integrating for two protons which was assigned to ($-S-C\underline{H}_2-CH_3$). The triplet at δ 1.31 which should have been exhibited for three methyl protons ($-S-CH_2-C\underline{H}_3$) was merged with the other methyl signals in this region and therefore it was not displayed as a clear triplet. Methyl signals appeared at δ 1.2 (C10β-$C\underline{H}_3$), 0.66 (C13β-$C\underline{H}_3$), 1.0, 0.93 and 0.83 (other methyl protons). The structure (XCIV) for the compound m.p. 172° was further supported by its mass spectrum which showed fragment ions at m/z 445 and 444 arising due to the loss of an oxygen atom and a hydroxy radical from the molecular ion. This fragmentation mode is characteristic of oxime function. Beside this a fragment ion at m/z 400 was due to the loss of $-SCH_2CH_3$ moiety. On the basis of the above data, the product was formulated as 5-ethylmercapto-5α-cholestan-6-one oxime (XCIV).

* This structure was chemically supported by its desulphurization[41] with Raney nickel, which provided 5α-cholestan-6-one oxime (XCV), m.p. 203° (reported[42] m.p. 204°).

The compound (XCIV) on treatment with Ac_2O/Py provided 5-ethylmercapto-5α-cholestan-6-one oxime-N-acetate (XCVI), m.p. 84°. The compound was analysed correctly for $C_{31}H_{53}NO_2S$

and gave positive sodiun nitroprusside test for sulphur. Its IR spectrum exhibited bands at 1735 ($0\underline{C}O\text{-}CH_3$), 1640 (C=N), 1410 (C-S def.) and 1230-1240 cm^{-1} (C-S wag., acetate). The NMR spectrum gave signals at δ 3.10 (m, C7-$\underline{H}_2$), 2.1 (s, -OCO-$C\underline{H}_3$), 2.2 (m, -S-$C\underline{H}_2$-CH_3), and 1.3 (t, S-CH_2-$C\underline{H}_3$). Methyl signals were seen at δ 0.96 (C10β-$C\underline{H}_3$), 0.86 and 0.66 (C13β-$C\underline{H}_3$). On the basis of above elemental and spectral analysis it was clear that the -OH group of the oxime was acetylated, indicated in NMR by the disappearance of a signal for -O$\underline{H}$ proton and emergence of a singlet at δ 2.1 for the -N-C(=O)-$C\underline{H}_3$ protons.

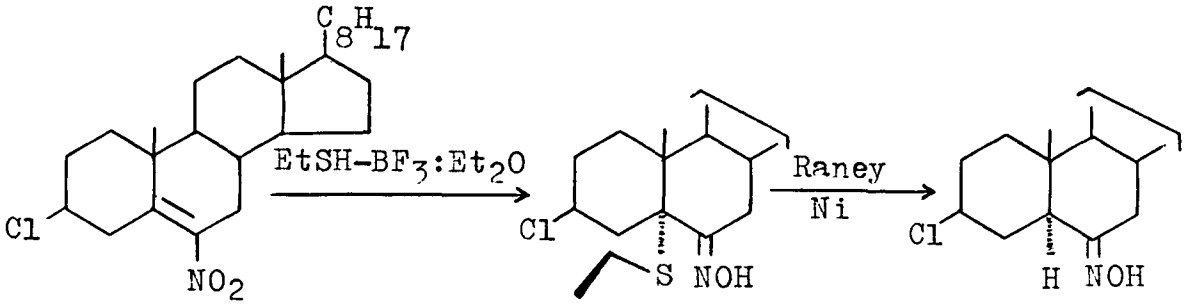


(XCIV) (XCVI)

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) with ethanethiol

3β-Chloro-6-nitrocholest-5-ene (LXXVIII) was treated with ethanethiol in dichloromethane using BF_3-etherate as a

catalyst. A compound, m.p. 180°, was obtained.



(LXXVIII) (XCVII) (LXXX)

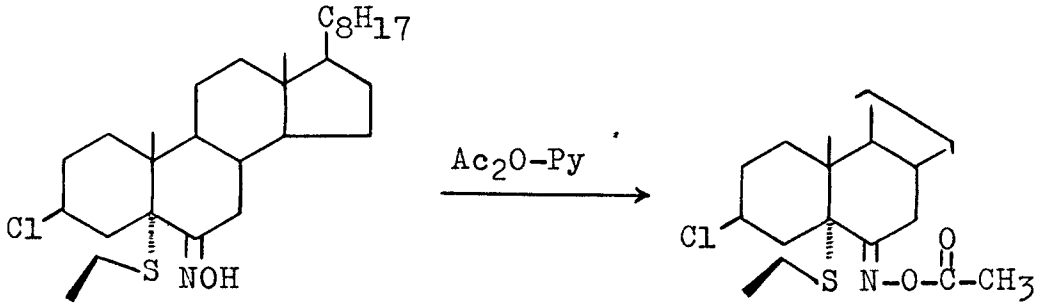
Characterization of the compound, m.p. 180° as 3β-chloro-5-ethymercato-5α-cholestan-6-one oxime (XCVII)

The mass spectrum of the compound (XCVII), m.p. 180° gave molecular ion peaksat m/z 495/497 and was analysed for $C_{29}H_{50}NOSCl$. The compound gave positive sodium nitroprusside test for sulphur. The IR spectrum of the compound displayed bands at 3300-3100 cm^{-1} for -OH and 1640 cm^{-1} for C=N absorptions. More absorption bands were exhibited at 1435 (C-S, def.), 1240 (C-S, wag.) and 730 cm^{-1} (C-Cl). The NMR spectrum of the compound displayed a broad singlet at δ 9.0 for =NO<u>H</u> which disappeared on D_2O shake. The multiplets were exhibited at δ 4.5 (C3α-<u>H</u>), 3.15 (C7-<u>H_2</u>) and 2.3 (-S-C<u>H_2</u>-CH_3) The triplet for -S-CH_2-C<u>H_3</u> was displayed at δ 1.33. The configuration of thioether group attached to C5 was decided on

the basis of half band width ($W\frac{1}{2}$) of the C3 proton which was found to be 17 Hz. This clearly indicates that the C3 proton is axial (α) and the ring juction A/B is trans. Therefore, the thioether linkage at C5 is axial or α- oriented[43]. Methyl signals were seen at δ 1.30 (C10β-$C\underline{H}_3$), 1.0, 0.9 and 0.83 (other methyl protons). The mass spectrum of the compound gave fragment ion peaks at m/z 478/480 and 479/481 which were due to the loss of -OH and oxygen atom respectively. Another significant ion peaks were at m/z 434/436 arising due to the loss of -S-CH_2-CH_3 moiety from the molecular ions which further supported the proposed structure. The elemental and spectral analysis established the structure of the compound 3β-chloro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII). The structure of the compound (XCVII) was supported chemically by its desulphurization with Raney nickel which provided 3β-chloro-5α-cholestan-6-one oxime (LXXX), m.p. 173-175° (reported[44] m.p. 175°).

The compound (XCVII) was acetylated with Ac_2O/Py to afford 3β-chloro-5-ethylmercapto-5α-cholest-6-one oxime-N-acetate (XCVIII) m.p. 116°. The elemental analysis of the product corresponded to $C_{31}H_{52}NO_2SCl$ and gave positive sodium nitroprusside test for sulphur. Its IR spectrum exhibited characteristic bands at 1735 (-O$\underline{C}$O$\underline{C}H_3$), 1640 (C=N), 1420 (C-S def.) and 1235-1240 cm^{-1} (C-S wag., acetate). The appearance

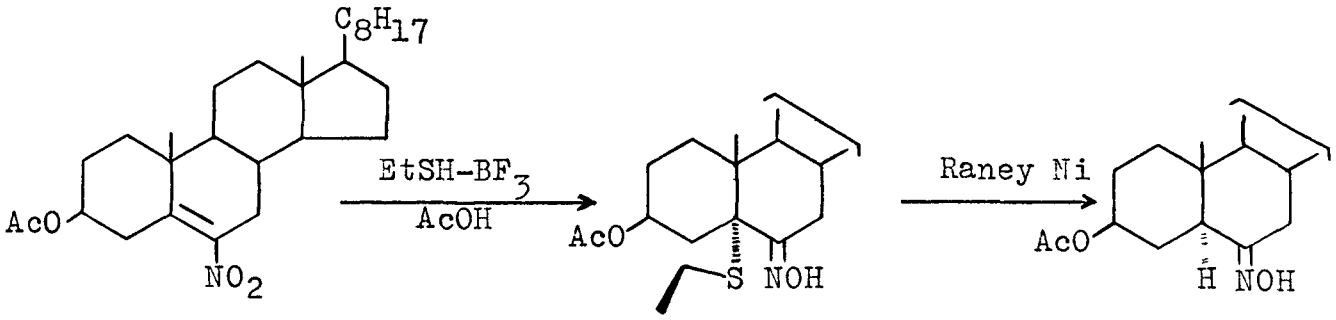
of a band at 1735 cm^{-1} indicated that the acetylation has taken place at =NOH. It was further confirmed by the disappearance of -OH assorption band. The NMR spectrum also supported and confirmed the above structure. It displayed signal at δ 4.5 (m, $W\frac{1}{2}$ = 17 Hz, C3α-H) which suggested that the A/B ring junction was still trans. The peak at δ 2.1 was assigned to -O-CO-CH_3 protons. The multiplets at δ 3.2 and δ 2.35 were assigned to C7-H_2 and S-CH_2-CH_3 respectively. A triplet appeared at δ 1.3 for S-CH_2-CH_3 protons. Methyl signals were observed δ 1.2 (C10β-CH_3), 0.6 (C13β-CH_3) and 1.0 and 0.9 (other methyl protons).



(XCVII) (XCVIII)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) with ethanethiol

3β-Acetoxy-6-nitrocholest-5-ene (LXXXI) was allowed to react with ethanethiol under the conditions described earlier. The TLC monitoring of the reaction mixture showed one product, which was worked up and a compound m.p. 181° was crystallized from acetonitrile.



(LXXXI) (LXXXVIIIa) (LXXXVIIIb)

Characterization of the compound, m.p. 181° as 3β-acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime(LXXXVIIIa)

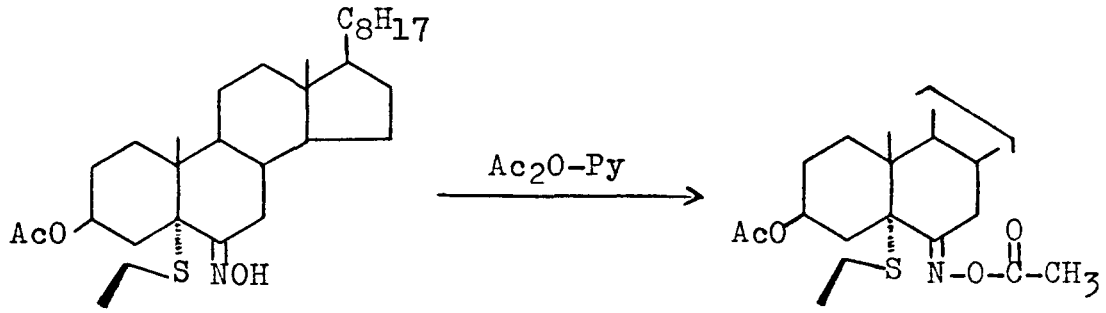
Microanalysis of the product, m.p. 181° gave the molecular composition as $C_{31}H_{53}NO_3S$ (M^+ 519) and gave positive sodium nitroprusside test for sulphur. The mass spectrum of the compound gave a molecular ion peak at m/z 519. The

IR spectrum exhibited characteristic broad band at 3300-3100 cm^{-1} for hydroxy group. Acetate group was shown by carbonyl absorption at 1720 cm^{-1} and oxime carbon nitrogen double bond at 1645 cm^{-1}. An absorption peak of medium intensity, displayed at 1400 cm^{-1} was assigned to carbon-sulphur deformation frequency and similarly another band at 1230-1215 cm^{-1} appeared for carbon-sulphur wagging absorption frequency. The NMR spectrum displayed a broad singlet at δ 9.05 for hydroxy proton which disappeared on exchange with D_2O. Multiplets appeared at δ 5.4 (C3α-$\underline{H}$), δ 3.15 (C7-$\underline{H}_2$) and at δ 2.3 which was assigned to methylene protons attached to sulphur atom. A singlet was displayed at δ 2.0 for the acetate methyl protons and a triplet at δ 1.35 for the methyl protons of the ethyl group attached to sulphur atom. The stereochemistry at C5 was decided on the basis of $W\frac{1}{2}$ value[43] of C3 proton which was 18 Hz showing C3α-H as axial A/B ring junction trans and the thioether linkage to be α-oriented (axial). Methyl proton signals were exhibited at δ 1.2 (C10β-$C\underline{H}_3$), 0.66 (C13β-$C\underline{H}_3$), 1.0, 0.95 and 0.85 (other methyl protons). The mass spectrum of the compound showed fragment ion peaks at m/z 502 and 503 which were due to the loss of OH and O respectively, from the molecular ion. These two fragment ions supported the presence of oximino function in the molecule. The loss of acetic acid from $M^{+\cdot}$ resulted into a peak at m/z 459. Another significant fragment ion peak at m/z 458 corresponded to the loss of $-SCH_2CH_3$ moiety from the

parent ion. Thus the structure of the compound (LXXXVIIIa) was assigned as 3β-acetoxy-5-ethylmercapto-5α-cholest-6-one oxime.

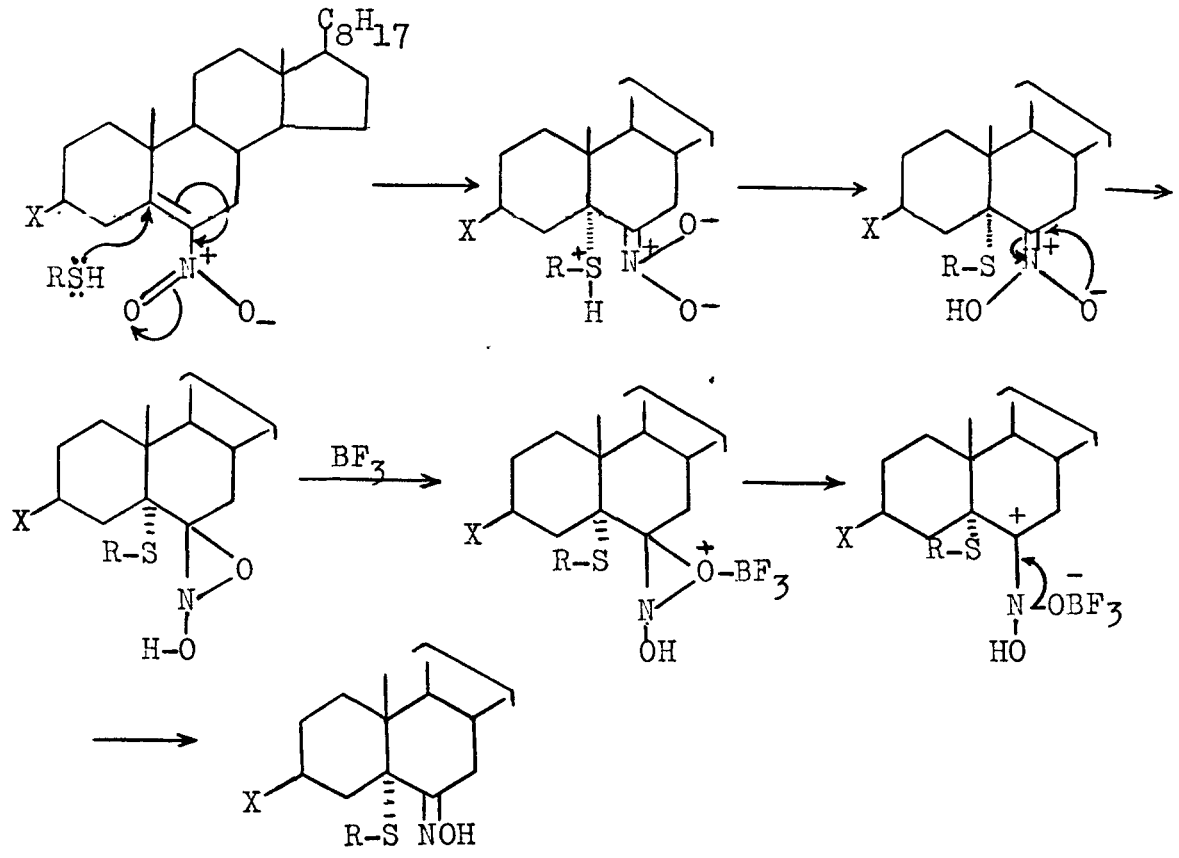
The chemical support for the proposed structure was given by desulphurization reaction with Raney nickel which afforded 3β-acetoxy-5α-cholestan-6-one oxime (LXXXVIIIh), m.p. 200° (reported[45] m.p. 201°).

The compound (LXXXVIIIa) on treatment with acetic anhydride and pyridine was converted to 3β-acetoxy-5-ethyl-mercapto-5α-cholest-6-one oxime-N-acetate (XCIX), m.p. 99-100°. The compound (XCIX) analysed correctly for $C_{33}H_{55}NO_4S$ gave positive sodium nitroprusside test for sulphur. IR spectrum exhibited bands at 1740-1735 cm^{-1} for two keto groups ($-O\underline{C}OCH_3$ and $-N-O-\underline{C}O-CH_3$). The other characteristic bands were displayed at 1640 (C=N), 1440 (C-S def.), 1240-1235 and 1030 cm^{-1} (C-S wag., acetate). The NMR spectrum displayed a multiplet at δ 5.4 ($W\frac{1}{2}$ = 18 Hz, C3α-$\underline{H}$) suggesting that the thioether group is axial. Two singlets were seen for two methyl groups at δ 2.1 ($-N-COC\underline{H}_3$) and 2.0 ($-OCOC\underline{H}_3$). A triplet at δ 1.3 was appeared for $-S-CH_2-C\underline{H}_3$. Methyl signals were seen at δ 1.21 (C10β-$C\underline{H}_3$), 0.65 (C13β-$C\underline{H}_3$) and at δ 1.0, .96 (other methyl protons).



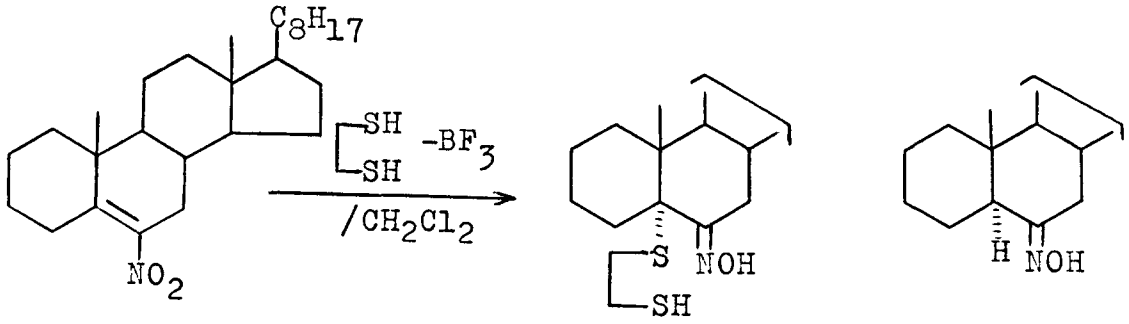
(LXXXVIIIa) (XCIX)

The probable mechanistic pathway suggested for the above transformation has been shown below.



B. Reaction of 6-nitrocholest-5-ene (LXXXIII) with 1,2-ethanedithiol

6-Nitrocholest-5-ene (LXXXIII) was treated with 1,2-ethanedithiol in dichloromethane and BF_3-etherate. The reaction was monitored with TLC. After completion of the reaction the reaction mixture was worked up in usual manner and chromatographed over silica gel to afford an amorphous solid compound.



(LXXXIII) (C) (XCV)

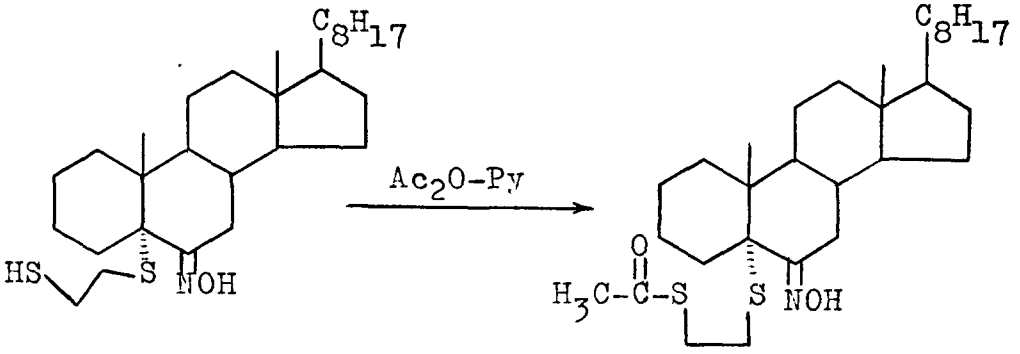
Characterization of the amorphous solid compound as 5α-(2'-thiohydroxythioethoxy)cholestan-6-one oxime (C)

The elemental analysis of the compound (C) corresponded to the formula $C_{29}H_{51}NOS_2$. It gave positive sodium nitroprusside test for sulphur. The IR spectrum exhibited strong bands at 3285 cm^{-1} for hydroxy function and a band of medium intensity for C=N, at 1640 cm^{-1}. The C-S absorption bands were at 1415 (def.) and 1240 cm^{-1} (wag.). The IR spectrum

clearly indicated the presence of an oxime group in the molecule, which was further confirmed on the basis of NMR spectrum which displayed a broad singlet at δ 9.35 for -O<u>H</u>. It disappeared on D_2O addition. It is pertinent to mention that hydrogen bonded with sulphur (-S<u>H</u>) appears around δ 1.6-1.2 which gets merged in methylene envelope of steroid framework[43]. The characteristic signal of four methylene protons was observed at δ 2.6 (-S-C<u>H</u>$_2$-C<u>H</u>$_2$-S-) as a multiplet. Methyl signals appeared at δ 0.9 (C10β-C<u>H</u>$_3$), 0.70 (C13β-C<u>H</u>$_3$), 0.83 (other methyl protons). From the above spectral and elemental analysis data, the product was formulated as 5α-(2'-thiohydroxy-thioethoxy) cholestan-6-one oxime (C). This structure was further supported by its desulphurization with Raney nickel, which provided 5α-cholestan-6-one oxime (XCV), m.p. 202-203° (reported[42] m.p. 204°).

The compound (C) was acetylated by acetic anhydride and pyridine and purified by column chromatography to give 5α-(2'-thioacetylthioethoxy)cholestane-6-one oxime (CI). The elemental analysis of the pure TLC homogeneous product corresponded to the formula $C_{31}H_{53}NO_2S_2$. The compound gave positive sodium nitroprusside test for sulphur. The IR spectrum showed characteristic peak for -OH group at 3300-3100 cm^{-1}. This suggested that hydroxy group was not acetylated during the reaction. Absorption bands were also seen at 1735 (-S-<u>C</u>(=O)-CH$_3$), 1635 (C=N), 1410 (C-S def.) and 1230-1220 cm^{-1}

(C-S wag., acetate). The NMR spectrum displayed signals at δ 2.66 (m, -S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 2.13 (s, -S-C(=O)-C$\underline{H}_3$), 0.9 (C10β-C$\underline{H}_3$), 0.66 (C13β-C$\underline{H}_3$) and 0.83 (other methyl protons). The elemental analysis and spectral study clearly indicated that it was the thiol group which was acetylated. On the basis of above data, the compound (CI) was characterized as 5α-(2'-thioacetylthioethoxy)cholestan-6-one oxime (CI).

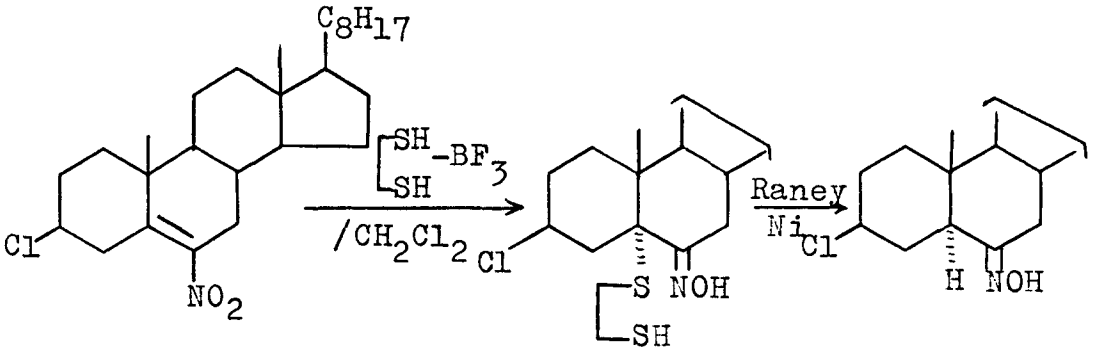


(C) (CI)

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) with 1,2-ethanedithiol

3β-Chloro-6-nitrocholest-5-ene (LXXVIII) was allowed to react with 1,2-ethanedithiol in the presence of BF_3-etherate in dichloromethane. The reaction was monitored with TLC. After the total consumption of the starting material the

reaction mixture was worked up and column chromatographed over silica gel to give an amorphous solid compound.



(LXXVIII) (CII) (LXXX)

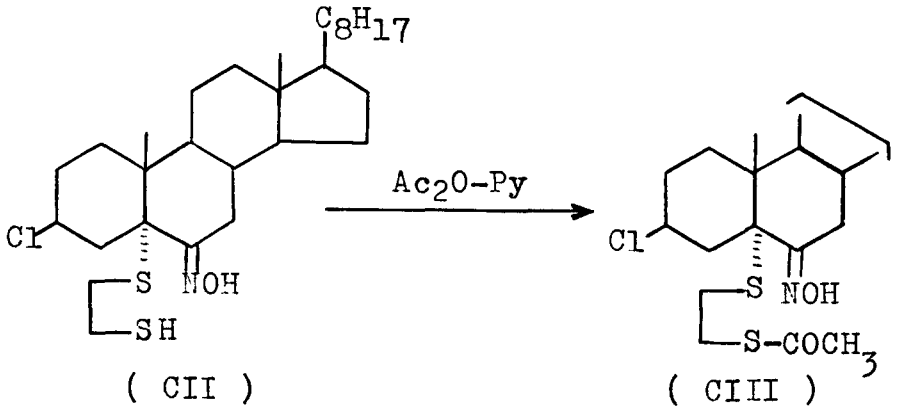
Characterization of the amorphous solid compound as 3β-chloro-5α-(2'-thiohydroxythioethoxy)cholestan-6-one oxime (CII)

The compound (CII) was analysed correctly for $C_{29}H_{50}NOS_2Cl$. It gave positive Beilstein test for halogen and positive sodium nitroprusside test for sulphur. The IR spectrum of the compound exhibited strong absorption bands at 3260 for hydroxy group, 1630 (C=N), 1410 (C-S def.), 1235 (C-S wag.) and 730 cm^{-1} (C-Cl). IR spectrum clearly supports the presence of an oximino group and sulphur moiety which was further illustrated by NMR spectroscopy. The

NMR spectrum showed a broad singlet for hydroxy proton at δ 9.2 which disappeared on D_2O shake. The signal of C3 proton decided the configuration of the thioether orientation at C5. C3 Proton appeared as a multiplet at δ 4.5 ($W\frac{1}{2}$ = 17 Hz) indicating that it is as axial, A/B ring junction trans and the thioether group was attached axially (α) to C5. The four methylene protons -S-$C\underline{H}_2$-$C\underline{H}_2$-SH were displayed at δ 2.7 as a multiplet. Methyl signals were seen at δ 1.06 (C10β-$C\underline{H}_3$), 0.66 (C13β-$C\underline{H}_3$), 0.93 and 0.83 (other methyl protons). Thus the compound was assigned the structure 3β-chloro-5α-(2'-thiohydroxythioethoxy)cholestan-6-one oxime (CII), which was further supported by its desulphurization with Raney nickel providing 3β-chloro-5α-cholestan-6-one oxime (LXXX) m.p. 174° (reported[44] m.p. 175°).

The compound (CII) on treatment with pyridine and acetic anhydride furnished an amorphous solid compound which was characterized as 3β-chloro-(2'-thioacetylthioethoxy) cholestan-6-one oxime (CIII). The compound (CIII), analysed correctly for $C_{31}H_{52}NO_2S_2Cl$ and gave positive Beilstein test for halogen and positive sodium nitroprusside test for sulphur. The IR spectrum of the compound exhibited absorption band at 3300 cm^{-1} for hydroxyl group. Acetate keto group was shown by a band at 1740 cm^{-1}. Carbon-nitrogen bond of oxime

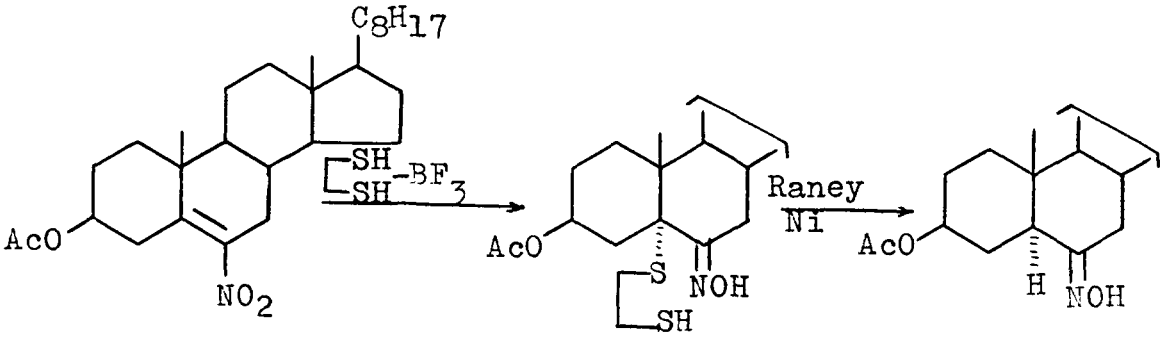
showed its absorption at 1640 cm^{-1}. Cabron-sulphur deformation and wagging absorption bands appeared at 1420 and 1230 cm^{-1} respectively. The IR spectrum itself gave the strong evidence that the acetylation has taken place at thiol group and not at hydroxy group of oxime which is still giving its strong band at 3300 cm^{-1}. The NMR spectrum of the compound further proved the point. It displayed a multiplet at δ 4.5 ($W\frac{1}{2}$ = 18 Hz) for C3 proton suggesting that it is attached axially to the C3 thereby proving that A/B ring junction is trans. A multiplet appeared for four methylene protons in the thioacetylthioethoxy group at δ 2.77. A singlet for three protons at δ 2.1 was assigned to the methyl protons of acyl group attached to sulphur. The broad singlet at δ 9.7 was due to hydroxy proton which disappeared on exchange with D_2O. Methyl signals appeared at δ 1.07 ($C10\beta-\underline{CH}_3$), 0.67 ($C13\beta-\underline{CH}_3$), 0.94 and 0.86 (other methyl protons).



(CII) (CIII)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) with 1,2-ethanedithiol

The reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) with 1,2-ethanedithiol was carried out as discussed earlier. TLC examination of the reaction mixture revealed one product which was purified by column chromatography to yield an amorphous solid compound.



(LXXXI) (CIV) (LXXXIII)

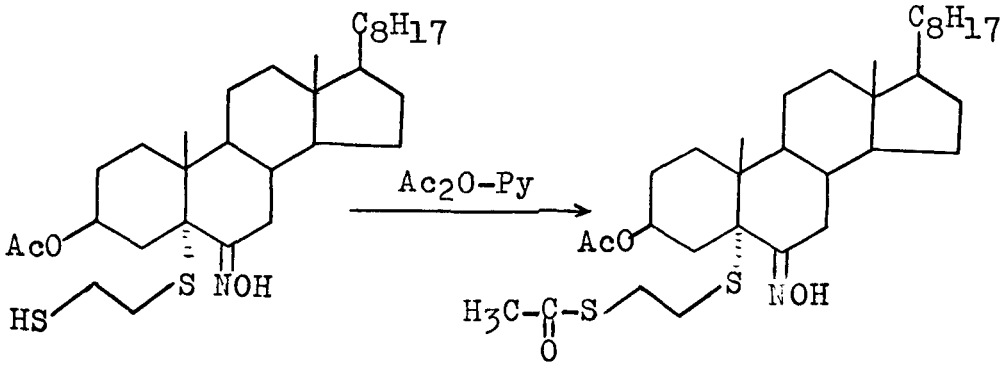
Characterization of the amorphous solid compound as 3β-acetoxy-5α-(2'-thiohydroxythioethoxy)cholestan-6-one oxime (CIV)

The elemental analysis of the compound (CIV) corresponded to the formula $C_{31}H_{53}NO_3S_2$ and it gave positive sodium nitroprusside test for sulphur. The compound had the characteristic IR absorption bands at 3280 (=N-OH), 1740 ($-O-\overset{O}{\overset{\|}{C}}-CH_3$) and 1630 cm^{-1} (C=N) oxime. The carbon-sulphur deformation

and wagging absorption were shown by medium intensity peaks at 1430 and 1230 cm^{-1} respectively. The NMR spectrum showed a broad signal at δ 9.2 for hydroxy proton which disappeared on D_2O shake. C3 Proton appeared as a multiplet at δ 5.4 ($W\frac{1}{2}$ = 18 Hz, C3α-H) suggesting that the ring junction is trans and thioether linkage at C5 is axial. The four methylene protons of thiohydroxythioethoxy (-S-CH_2-CH_2-S-) group were displayed as multiplet at δ 2.75. Methyl protons of acetate group appeared as a singlet at δ 2.05. Methyl protons were shown at δ 0.90 (C10β-CH_3), 0.66 (C13β-CH_3) and 0.84 (other methyl protons). Thus on the basis of IR, NMR and elemental analysis the compound was characterized as 3β-acetoxy-5α-(2'-thiohydroxythioethoxy)cholestan-6-one oxime (CIV). The structure of the compound (CIV) was further supported by its desulphurization with Raney nickel which provided 3β-acetoxy-5α-cholestan-6-one oxime (LXXXVIIIh), m.p. 199-200° (reported[45] m.p. 201°).

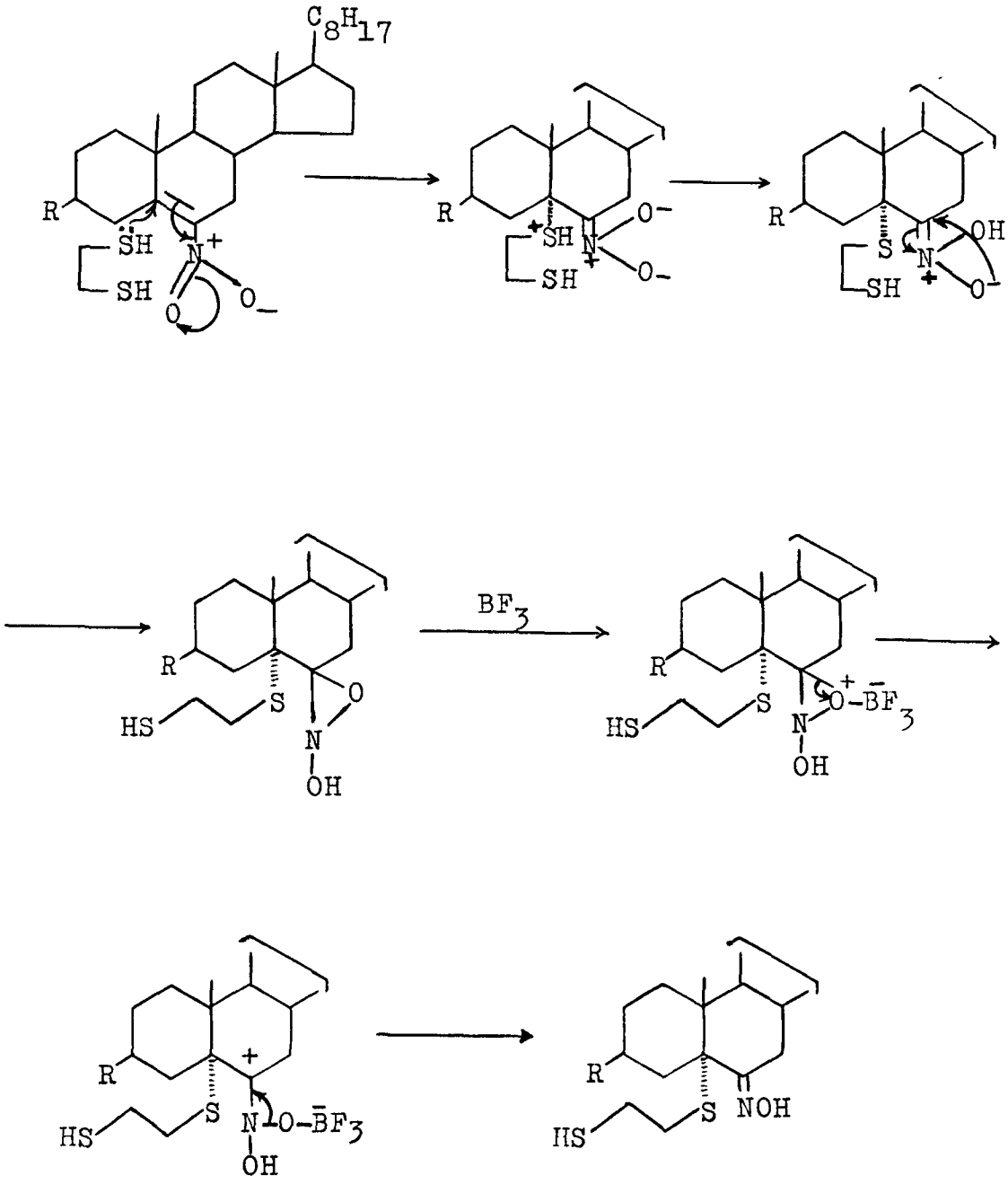
The compound (CIV) was treated with Ac_2O/Py to afford 3β-acetoxy-5α-(2'-thioacetylthioethoxy)cholestan-6-one oxime (CV) as an amorphous solid. The compound analysed for $C_{33}H_{55}NO_4S_2$ gave positive sodium nitroprusside test for sulphur. The IR spectrum displayed absorption band 3300 cm^{-1} for hydroxy group. Broad bands at 1740-1735 cm^{-1} were assigned to two carbonyls of acetate and S-acetyl groups.

Oxime function was represented by carbon-nitrogen double bond absorption at 1635 cm^{-1}. A medium intensity band at 1420 cm^{-1} was due to carbon-sulphur deformation and 1240 for C-S wagging frequencies. The NMR spectrum exhibited a multiplet at δ 5.5 ($W\frac{1}{2}$ = 18 Hz) for C3 proton indicating that its orientation is axial, carbon-sulphur linkage at C5 is axial and A/B ring junction is trans. Another multiplet at δ 2.8 for four protons was assigned to methylene protons of thioethoxy group. Two singlets each for three protons at δ 2.15 and δ 2.05 were ascribed for methyl protons of acetate and S-acetyl groups. Methyl signals were displayed at δ 0.9 (C10β-CH_3, along with other methyl protons) and 0.66(C13β-CH_3). The elemental and spectral analysis established the structure of the compound as 3β-acetoxy-5α-(2'-thioacetylthioethoxy) cholestan-6-one oxime (CV).



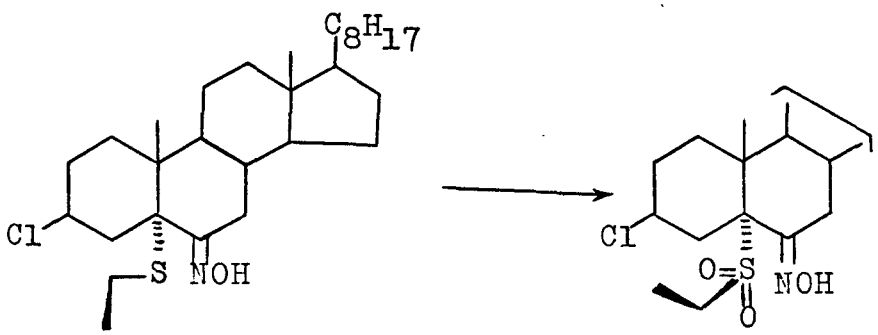
(CIV) (CV)

The following mechanism was suggested for the above transformations.



C. Reaction of 3β-chloro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII) with m-chloroperbenzoic acid

3β-Chloro-5-ethylmercapto-5α-cholest-6-one oxime (XCVII) was treated with m-chloroperbenzoic acid in dichloromethane at 0°C. The reaction mixture was kept at room temperature for 20 min. Usual work up in dichloromethane provided an amorphous solid compound.



(XCVII) (CVI)

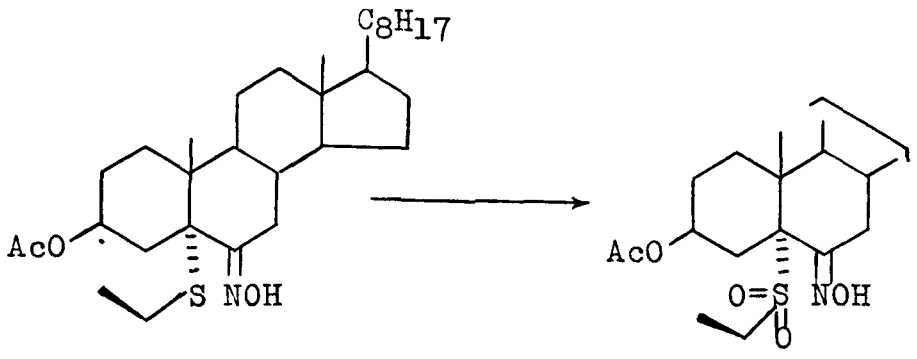
Characterization of the amorphous solid compound as 3β-chloro-5-ethylsulphone-5α-cholestan-6-one oxime (CVI)

The compound was analysed for $C_{29}H_{50}NO_3SCl$. It gave positive Beilstein test for halogen and positive sodium nitroprusside test for sulphur. The IR spectrum showed absorption bands at 3300 (-OH), 1630 cm^{-1} (C=N). These two absorption bands confirmed the presence of oximino group in

the compound. Strong absorption bands appeared for $-SO_2-$ stretching frequencies at 1300-1280 and 1140 cm^{-1}[143a]. The NMR spectrum of the compound displayed a broad singlet at δ 9.0 for -O<u>H</u> proton which disappeared on exchange with D_2O and a signal at δ 4.5 (m, $W\frac{1}{2}$ = 16 Hz, 3α-<u>H</u>). A triplet was seen at δ 1.25 for $-\overset{O}{\overset{\|}{S}}(=O)-CH_2-C\underline{H}_3$ protons. Methylene protons of $-\overset{O}{\overset{\|}{S}}(=O)-C\underline{H}_2CH_3$ appeared as multiplet at δ 2.5 and merged in methylene envelope of steroidal framework. Other methyl signals were seen at δ 0.9 (C10β-C<u>H</u>$_3$), 0.65 (C13β-C<u>H</u>$_3$). The elemental analysis and the spectral data suggested the structure of the compounds as 3β-chloro-5-ethylsulphone-5α-cholestan-6-one oxime (CVI).

<u>Reaction of 3β-acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime (LXXXVIIIa) with m-chloroperbenzoic acid</u>

The compound (LXXXVIIIa) was treated with m-chloroperbenzoic acid in dichloromethane at 0°C. The reaction mixture was kept at room temperature for 20 min. Usual work up yielded an amorphous solid compound.



(LXXXVIIIa) (CVII)

Characterization of the amorphous solid compound as 3β-acetoxy-5-ethylsulphone-5α-cholestan-6-one oxime (CVII)

The compound (CVII) was analysed correctly for $C_{31}H_{53}NO_5S$. The IR spectrum of the compound exhibited characteristic bands at 3440 (-OH) and 1640 cm^{-1} (C=N), due to oximino group in the molecule. Sulphone group showed its stretching absorption bands at 1310, 1165 and 1125 cm^{-1} and acetate group was confirmed due to a band at 1720 cm^{-1}. The NMR spectrum of the compound displayed a broad singlet at δ 9.2 (exchangeable with D_2O) and a multiplet at δ 5.4 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H). Methylene protons of $-\overset{O}{\overset{\|}{\underset{O}{\|}}}S-CH_2CH_3$ appeared as multiplet at δ 2.54 and merged in the methylene envelope of steroidal framework. The other signals in the NMR spectrum were observed at δ 2.0 ($-O-COCH_3$), 0.9 ($C10\beta-CH_3$), 0.66 ($C13\beta-CH_3$) and 0.81 (other methyl protons).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer 237 and Unichem SP300 *spectrophotometeres. The NMR spectra were run in* $CDCl_3$ *on* Varian A60 instrument with TMS as internal standard. Mass spectra were run on JEOL JMS D300 mass spectrophotometer at the source temperature of 120°C. Thin layer chromatographic plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. NMR values were gi en in δ ppm (s, singlet; d, doublet; t, triplet; br, broad; m , multiplet centred at). IR values are given in cm^{-1} (s, strong; m, medium; w, weak; br, broad).

5α-Chloestan-6-one

6-Nitrocholest-5-ene (6 g) was dissolved in warm glacial acetic acid (120 ml) and zinc dust (12 g) was gradually added with shaking. The suspension was heated under reflux for 4 hrs, and water (12 ml) was added now and then during the course of reaction. The hot solution was filtered to remove zinc powder, cooled to room temperature and diluted with a

large excess of ice cooled water. The precipitate thus obtained was taken in ether and the ethereal solution was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave the ketone as an oil which was crystallized from ethanol as thin plates (3.5 g), m.p. 96-98° (reported[46], m.p. 98-100°).

5α-Cholestan-6-one oxime (XCV)

5α-Cholestan-6-one (3 g), hydroxylamine hydrochloride (3 g) and sodium acetate trihydrate (6 g) were dissolved in ethanol (180 ml) and the mixture was refluxed on a water bath for two hrs. After the completion of the reaction, the solvent was removed under reduced pressure and the reaction mixture was diluted with ice cooled water. The crude oxime thus obtained was filtered under suction, air dried and recrystallized from ethanol to give 5α-cholestan-6-one oxime (XCV) (2.5 g), m.p. 198-200° (reported[42], m.p. 204°).

3β-Chloro-5α-cholestan-6-one

To a solution of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) (12 g) in hot glacial acetic acid (240 ml), zinc dust (24 g) was added gradually in small portions with shaking. The

suspension was heated under reflux for four hours and water (24 ml) was added at regular intervals during the course of the reaction. The hot solution was filtered to remove zinc and the filtrate was cooled to room temperature and diluted with a large excess of ice cooled water. The organic matter was extracted with ether. The ethereal solution was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvents gave an oil which was crystallized from methanol to give the ketone(yield 72%) (8.7 g), m.p.128-129° (reported[47], m.p. 129-130°).

3β-Chloro-5α-cholestan-6-one oxime (LXXX)

3β-Chloro-5α-cholestan-6-one (3 g) in ethanol (180 ml), hydroxylamine hydrochloride (7.5 g) and sodium acetate trihydrate (12 g) were mixed together and the mixture was refluxed for two hrs. Excess of the solvent was removed under reduced pressure and the residue was diluted with ice cooled water. The crude oxime thus obtained was filtered under suction, washed with water, air dried and recrystallized from ethanol (2 g), m.p. 173-175° (reported[44], m.p. 175°).

3β-Acetoxy-5α-cholestan-6-one

3β-Acetoxy-6-nitrocholest-5-ene (LXXXI) (3 g) was dissolved in glacial acetic acid (125 ml) by warming the mixture

and zinc dust (6 g) was added in small portions with shaking. The suspension was heated under reflux for four hrs. and water (6 ml) was added now and then during the course of the reaction. The hot solution was filtered to remove zinc, cooled to room temperature and diluted with a large excess of ice cooled water. The white precipitate thus obtained was taken in ether and the ethereal solution was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was crystallized from methanol to give the ketone (2.1 g), m.p. 128-129° (reported[48], m.p. 127-128°).

3β-Acetoxy-5α-cholestan-6-one oxime (LXXXVIIIh)

A mixture of 3β-acetoxy-5α-cholestan-6-one (3 g), hydroxylamine hydrochloride (3 g), sodium acetate trihydrate (6 g) and ethanol (120 ml) was heated under reflux for 2 hrs. Excess of the solvent was removed by distillation under reduced pressure and the residue was diluted with ice cooled water. The crude oxime thus obtained was filtered under suction, washed with water, air dried and recrystallized from ethanol (2 g), m.p. 200° (reported[45], m.p. 201°).

Reaction of 6-nitrocholest-5-ene (LXXXIII) with ethanethiol: 5-Ethylmercapto-5α-cholestan-6-one oxime (XCIV)

A solution of 6-nitrocholest-5-ene (LXXXIII) (1 g) in dichloromethane (10 ml) was allowed to react with ethanethiol (10 ml) and BF_3-etherate (9 equiv.) as catalyst at 0°C. TLC monitoring of the reaction mixture showed that the reaction was completed in 72 hrs. After adding few drops of methanol to the reaction mixture, the solvent and reagent were removed under reduced pressure and the residue was taken in ether. The ethereal layer was washed successively with brine, water and dried over anhydrous sodium sulphate. Evaporation of the solvent left an viscous crude material which was recrystallized from acetonitrile to afford 5-ethylmercapto-5α-cholestan-6-one oxime (XCIV) (930 mg), m.p. 172°.

Analysis Found : C, 75.45; H, 11.05; N, 3.02

$C_{29}H_{51}NOS$ requires : C, 75.48; H, 11.06; N, 3.03%.

MS : m/z 461 (M^+), 444 (M^+-OH), 400 (M^+-SC_2H_5).

IR : $\nu_{max.}$ 3300-3100 (-OH), 1640 (C=N), 1440 (CH_2-S def.), 1240 cm^{-1} (CH_2-S wag.).

^{1}H-NMR : δ 9.7 (brs, -OH, disappeared on D_2O exchange), 3.06 (m, C7-H_2), 2.2 (m, -S-CH_2-CH_3), 1.31 (t, -S-CH_2-CH_3), 1.2 (C10β-CH_3), 0.66 (C13β-CH_3), 1.0 , 0.93 and 0.83 (other methyl protons).

Desulphurization of compound (XCIV)

The compound (XCIV) (100 mg) on desulphurization with Raney nickel (1 g) in ethanol (100 ml) on refluxing for 20 hrs afforded 5α-cholestan-6-one oxime (XCV), m.p. 203° (reported[42], m.p. 204°).

Acetylation of XCIV

A mixture of 5-ethylmercapto-5α-cholestan-6-one oxime (XCIV) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was heated on a water bath for one hr. The reaction mixture was poured into ice cooled water and preceipitate thus obtained was extracted with ether. The ethereal layer was washed successively with water, $NaHCO_3$ solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided XCVI (75 mg), recrystallized from petroleum-ether, m.p. 84°.

Analysis Found : C, 73.93; H, 10.51; N, 2.70

$C_{31}H_{53}NO_2S$ requires : C, 73.95; H, 10.53; N, 2.78%.

IR : $\nu_{max.}$ 1735 ($-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1640 (C=N), 1410 ($CH_2$-S def.), 1230 (acetate, CH_2S wag.) and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 3.10 (m, C7-$\underline{H}_2$), 2.1 (s, $-O-\underset{\underset{O}{\|}}{C}-C\underline{H}_3$), 2.2 (m, $-S-C\underline{H}_2-CH_3$), 1.3 (t, $-S-CH_2-C\underline{H}_3$), 0.96 (C10β-$C\underline{H}_3$), 0.66 (C13β-$C\underline{H}_3$), 0.86 (other methyl protons).

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) with ethanethiol: 3β-Chlro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII)

3β-Chloro-6-nitrocholest-5-ene (LXXVIII) (1 g) was treated with ethanethiol (10 ml) and BF_3-etherate (9 equiv.) in dichloromethane (10 ml). Final work up yielded a semi-solid which was recrystallized from acetonitrile to give 3β-chloro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII) (950 mg), m.p. 180°.

Analysis Found : C, 70.20; H, 10.08; N, 2.81

$C_{29}H_{50}NOSCl$ requires : C, 70.23; H, 10.10; N, 2.8%.

MS : m/z 495/497 (M^+), 478/480 (M^+-OH), 479/481 (M^+-O), 459 (M^+-HCl), 434/436 (M^+-S-C_2H_5).

IR : $\nu_{max.}$ 3300-3100 (-OH), 1640 (C=N), 1435 (CH_2-S, def.), 1240 (CH_2-S, wag.), 1030 (C-O) and 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 9.0 (br s, -OH, disappears on D_2O exchange), 4.5 (m, $W\frac{1}{2}$ = 17 Hz, C3α-H), 3.15 (m, C7-H_2), 2.3 (m, -CH_2-CH_3), 1.33 (t, -S-CH_2-CH_3, 1.3 (C10β-CH_3), 0.66 (C13β-CH_3), 1.0, 0.9 and 0.83 (other methyl protons).

Desulphurization of compound (XCVII)

The compound (XCVII) (100 mg) in absolute methanol (100 ml) was treated with Raney nickel (1 g) and the reaction

mixture was refluxed for 20 hrs. The suspension was filtered and the filtrate was evaporated to dryness. The compound was crystallized from ethanol (50 mg), m.p. 173-175° (reported[44], m.p. 175°). This product was found identical with 3β-chloro-5α-cholestan-6-one oxime (LXXX).

Acetylation of XCVII

A mixture of 3β-chloro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was heated on a water bath for one hr. The reaction mixture was poured in cold water and the precipitate thus obtained was extracted with ether. The ethereal layer was washed with water, $NaHCO_3$ solution (5%) and dried over anhydrous sodium sulphate. Removal of the solvent yielded XCVIII (80 mg) as semisolid which was crystallized from petroleum ether m.p. 116°.

Analysis Found : C, 69.12; H, 9.63; N, 2.57

$C_{31}H_{52}NO_2SCl$ requires : C, 69.14; H, 9.66; N, 2.60%.

IR : $\nu_{max.}$ 1735 ($-O-\underset{O}{\overset{\|}{C}}-CH_3$), 1640 (C=N), 1420 ($CH_2$-S def.), 1240 ($CH_2$-S wag.) and 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 4.5 (m, $W_{\frac{1}{2}}$ = 17 Hz, C3α-H), 2.1 (s, $-OCOCH_3$), 3.2 (m, C7-H_2), 2.35 (m, $-S-CH_2-CH_3$), 1.3 (t, $S-CH_2-CH_3$) 1.2 (C10β-CH_3), 0.6 (C13β-CH_3), 1.0 and 0.9 (other methyl protons).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) with ethanethiol: 3β-Acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime (LXXXVIIIa)

The reaction mixture of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) (1 g) with ethanethiol (10 ml) in dichloromethane (10 ml) using BF_3-etherate (9 equiv.) as catalyst at 0°C was kept at room temperature for 72 hrs. After adding few drops of methanol and evaporation of the solvent under reduced pressure, the reaction mixture was worked up in usual manner and the compound (LXXXVIIIa) was crystallized from acetonitrile (940 mg), m.p. 181°.

Analysis Found : C, 71.60; H, 10.19; N, 2.58;

$C_{31}H_{53}NO_3S$ requires : C, 71.67; H, 10.21; N, 2.60%.

MS : m/z 519 (M^+), 502 (M^+-OH), 459 (M^+-AcOH), 458 (M^+-S-C_2H_5).

IR : $\nu_{max.}$ 3300-3100 (-OH), 1720 (-O-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1645 (C=N), 1400 ($CH_2$-S def.), 1230-1215 ($CH_2$-S, wag. and acetate), 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 9.05 (br s, -OH, disappears on exchange with D_2O), 5.4 (m, $W\frac{1}{2}$ = 18 Hz, C3 α-H), 3.15 (m, C7-H_2), 2.3 (m, -S-CH_2-CH_3), 2.0 (s, -OCOCH_3), 1.35 (t, -S-CH_2-CH_3), 1.2 (C10β-CH_3), 0.66 (C13β-CH_3), 1.0, 0.95 and 0.85 (other methyl protons).

Desulphurization of compound (LXXXVIIIa)

The compound (LXXXVIIIa) (100 mg) on treatment with Raney-nickel (1 g) in absolute ethanol (100 ml) and refluxing for 20 hrs. provided 3β-acetoxy-5α-cholestan-6-one oxime (LXXVIIIb)(45 mg), m.p. 200° (reported[45], m.p. 201°).

Acetylation of (LXXXVIIIa)

A mixture of 3β-acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime (LXXXVIIIa) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was heated on a water bath for 1 hr. The reaction mixture was poured into cold water, extracted with ether and dried over anhydrous sodium sulphate. Removal of the solvent provided XCIX (75 mg), recrystallized from light petroleum, m.p. 99-100°.

Analysis Found : C, 74.80; H, 10.33; N, 2.61

$C_{33}H_{55}NO_4S$ requires : C, 74.85; H, 10.39; N, 2.64%.

IR : $\nu_{max.}$ 1740-1735 ($-N-\underset{\underset{O}{\|}}{C}-CH_3$ and $-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1640 (C=N), 1440 ($CH_2$-S, def.), 1240 ($CH_2$-S, wag, and acetate), 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 5.4 (m, $W_{\frac{1}{2}}$ = 18 Hz, C3α-H), 2.1 (s, $-N-\underset{\underset{O}{\|}}{C}-CH_3$), 2.0 (s, $-O-\underset{\underset{O}{\|}}{C}-CH_3$), 2.4 (m, $-S-CH_2-CH_3$), 1.3 (t, $-S-CH_2-CH_3$), 1.21 (C10β-CH_3), 0.65 (C13β-CH_3), 1.0 and 0.96 (other methyl protons).

Reaction of 6-nitrocholest-5-ene (LXXXIII) with 1,2-ethanedithiol: 5α-(2'-thiohydroxythioethoxy)-cholestan-6-one oxime(C)

To a solution of 6-nitrocholest-5-ene (1 g) in dichloromethane (15 ml), 1,2-ethanedithiol (2 ml) and BF_3-etherate (15 ml) were added at 0°C. The reaction mixture was kept at room temperature for 5 days. The progress of the reaction was monitored with the help of TLC. After completion of the reaction, the reaction mixture was worked up in chloroform after adding few drops of methanol. The organic layer was washed with brine and water. The solvent and reagent were removed under reduced pressure to yield a semisolid which was purified with column chromatography using petroleum and ether. The final product (C) was obtained as an amorphous solid (760 mg).

Analysis Found : C, 70.62; H, 10.16; N, 2.61

$C_{29}H_{51}NOS_2$ requires : C, 70.63; H, 10.17; N, 2.65%.

IR : $\nu_{max.}$ 3285 (-OH), 1640 (C=N), 1415 (CH_2-S def.), 1240 cm^{-1} (CH_2-S wag.).

^{1}H-NMR : δ 9.35 (br s, -OH, disappeared on D_2O exchange), 2.6 (m, -S-C<u>H</u>$_2$-C<u>H</u>$_2$-S), 0.9 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$) and 0.83 (other methyl protons).

Desulphurization of compound (C)

The compound (C) (100 mg) on treatment with Raney nickel (1 g) in absolute ethanol (100 ml) furnished 5α-cholestan-6-one oxime (XCV) (40 mg), m.p. 202° (reported[42], m.p. 202-203°).

Acetylation of C

The compound (C) (100 mg) was acetylated by dissolving it in purified pyridine (0.6 ml) and acetic anhydride (0.4 ml). The reaction was kept on a water bath for 1 hr. and the reaction mixture was poured in ice coold water and the compound was taken up in ether, washed with water, $NaHCO_3$ solution (5%), water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the amorphous solid (CI) (85 mg).

Analysis Found : C, 69.50; H, 9.88; N, 2.59

$C_{31}H_{53}NO_2S_2$ requires : C, 69.53; H, 9.90; N, 2.61%

IR : $\nu_{max.}$ 3300-3100 (-OH), 1735 ($-S-\underset{O}{\underset{\|}{C}}-CH_3$), 1635 (C=N), 1410 ($CH_2$-S def.) and 1230-1220 cm^{-1} (CH_2-S wag. and acetate).

^{1}H-NMR : δ 2.66 (m, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 2.13 (s, $-S-\underset{O}{\underset{\|}{C}}-C\underline{H}_3$), 0.9 (C10β-$C\underline{H}_3$), 0.66 (C13β-$C\underline{H}_3$) and 0.83 (other methyl protons).

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) with 1,2-ethanedithiol: 3β-Chloro-5α-(2'-thiohydroxythioethoxy)-cholestan-6-one oxime (CII)

A solution of 3β-chloro-6-nitrocholest-5-ene (LXXVIII) (1 g) in dichloromethane (15 ml), 1,2-ethanedithiol (2 ml) and BF_3-etherate (1.5 ml) were added at 0°C. The reaction was allowed to stand at room temperature for 5 days and was monitored with TLC. After completion of the reaction few drops of methanol was added and the reaction mixture was worked up in chloroform, washed with water, brine, water and dried over anhydrous sodium sulphate. The solvent and reagent were evoporated under reduced pressure. The crude material thus obtained was column chromatographed to purify amorphous solid compound (CII) (885 mg).

Analysis Found : C, 65.81; H, 9.45; N, 2.62

$C_{29}H_{50}NOS_2Cl$ requires : C, 65.97; H, 9.47; N, 2.65%.

IR : $\nu_{max.}$ 3260 (-OH), 1630 (C=N), 1410 (CH_2-S def.), 1235 (CH_2-S wag.) and 730 cm^{-1} (C-Cl).

^{1}H-NMR: δ 9.2 (br s, -OH, disappeared on D_2O exchange), 4.5 (m, $W\frac{1}{2}$ = 17 Hz, C3α-H), 2.7 (m, -S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 1.06 (C10β-C$\underline{H}_3$), 0.66 (C13β-C$\underline{H}_3$), 0.93 and 0.83 (other methyl protons).

Desulphurization of compound (CII)

The compound (CII) (100 mg) on desulphurization with Raney nickel (1 g) in ethanol gave 3β-chloro-5α-cholestan-6-one oxime (LXXX) (52 mg), m.p. 174° (reported[44], m.p. 175°).

Acetylation of CII

A mixture of 3β-chloro-5α-(2'-thiohydroxythioethoxy)-cholestan-6-one oxime (CII) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was heated on a water bath for 1 hr. The reaction mixture was poured into ice cooled water and worked up in usual manner. Removal of the solvent yielded CIII (80 mg) as an amorphous solid.

Analysis Found : C, 65.31; H, 9.11; N, 2.41

$C_{31}H_{52}NO_2S_2Cl$ requires : C, 65.37; H, 9.13; N, 2.46%

IR : $\nu_{max.}$ 3300 (-OH), 1740 (-S-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1640 (C=N), 1420 ($CH_2$-S def.), 1230 cm^{-1} (CH_2-S wag.).

^{1}H-NMR : δ 9.7 (br s, -O$\underline{H}$, exchangeable with D_2O), 4.5 (m, $W_{\frac{1}{2}}$ = 18 Hz, C3α-$\underline{H}$), 2.77 (m, -S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 2.1 (s, -S-$\underset{\underset{O}{\|}}{C}$-C$\underline{H}_3$), 1.07 (C10β-C$\underline{H}_3$), 0.94 and 0.86 (other methyl protons).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) with 1,2-ethanedithiol: 3β-Acetoxy-5α-(2'-thiohydroxythioethoxy)-cholestan-6-one oxime (CIV)

The similar reaction of 3β-acetoxy-6-nitrocholest-5-ene (LXXXI) (1 g) with 1,2-ethanedithiol in dichloromethane (15 ml) in the presence of BF_3-etherate (1.5 ml) was carried out as described earlier. Final work up yielded a crude material which was purified by column chromatography using petroleum and ether as eluting agent to provide an amorphous solid (CIV) (860 mg).

Analysis Found : C, 67.41; H, 9.55; N, 2.47

$C_{31}H_{53}NO_3S_2$ requires : C, 67.51; H, 9.61; N, 2.54%

IR : $\nu_{max.}$ 3280 (-O<u>H</u>), 1740 (-O-<u>C</u>(=O)-C<u>H</u>$_3$), 1630 (C=N), 1430 (CH_2-S def.), 1230-1225 (CH_2-S wag., acetate) and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 9.2 (br s, -O<u>H</u>, disappears on D_2O exchange), 5.4 (m, $W_{\frac{1}{2}}$ = 18 Hz, C3α-<u>H</u>), 2.75 (m, -S-C<u>H</u>$_2$-C<u>H</u>$_2$-S-), 2.05 (-O-C(=O)-C<u>H</u>$_3$), 0.90 (C10β-C<u>H</u>$_3$), 0.66 (C13β-C<u>H</u>$_3$), 0.84 (other methyl protons).

Desulphurization of compound (CIV)

The compound (CIV (100 mg) on usual treatment with Raney nickel (1 g) provided 3β-acetoxy-5α-cholestan-6-one oxime (LXXXVIIIh) (60 mg), m.p. 199-200° (reported[45], m.p. 201°).

Acetylation of CIV

A mixture of (CIV) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was heated on a water bath for 1 hr. The reaction mixture was poured in ice cooled water and taken up in ether. The ethereal layer was washed successively with water, sodium bicarbonate (5%), water and dried (anhydrous sodium sulphate). Removal of the solvent yielded CV (80 mg) as an amorphous solid.

Analysis Found : C, 66.81; H, 9.22; N, 2.40

$C_{33}H_{55}NO_4S_2$ requires : C, 66.77; H, 9.27; N, 2.36%

IR : $\nu_{max.}$ 3300 (-OH), 1740-1735 (-S-$\underset{\|}{\underline{C}}$-$CH_3$ and -O-$\underset{\|}{\underline{C}}$-$CH_3$), 1635 (C=N), 1420 ($CH_2$-S def.), 1240 ($CH_2$-S wag., acetate) and 1035 cm^{-1} (C-O).

^{1}H-NMR : δ 5.5 (m, $W_{\frac{1}{2}}$ = 18 Hz, C3α-$\underline{H}$), 3.0 (br s, -OH, exchangeable with D_2O), 2.8 (m, -S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 2.15 (s, S-$\underset{\|}{\underline{C}}$-C$\underline{H}_3$), 2.05 (s, -O-$\underset{\|}{\underline{C}}$-C$\underline{H}_3$), 0.9 (C10$\beta$-C$\underline{H}_3$), 0.66 (C13$\beta$-C$\underline{H}_3$).

Reaction of 3β-chloro-5-ethylmercapto-5α-cholestan-6-one oxime (XCVII) with m-chloroperbenzoic acid: 3β-Chloro-5-ethylsulphone -5α-cholestan-6-one oxime (CVI)

The compound (XCVII) (100 mg) was dissolved in dichloromethane (10 ml) and to this was added m-chloroperbenzoic acid

(2 moles) at 0°C. The reaction mixture was kept at room temperature for 20 min. The reaction mixture was worked up in usual manner and dried over anhydrous sodium sulphate. The solvent evaporation provided an amorphous solid (CVI) (85 mg).

Analysis Found : C, 66.11; H, 9.51; N, 2.70

$C_{29}H_{50}NO_3SCl$ requires : C, 66.03; H, 9.48; N, 2.65%.

IR : $\nu_{max.}$ 3300 (-CH), 1630 (C=N), 1300-1280 ($-SO_2-$, stretch.), 1140 ($-SO_2-$) and 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 9.0 (br s, -OH, exchangeable with D_2O), 4.5 ($W\frac{1}{2}$ = 16 Hz, C3α-H), 2.5 (m, $-\overset{O}{\overset{\|}{S}}\overset{O}{\overset{\|}{}}-CH_2-CH_3$), 1.25 (t, $-\overset{O}{\overset{\|}{S}}\overset{O}{\overset{\|}{}}-CH_2-CH_3$), 0.9 (C10β-$CH_3$), 0.65 (C13β-$CH_3$), 0.8 (other methyl protons).

Reaction of 3β-acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime (LXXXVIIIa) with m-chloroperbenzoic acid: 3β-Acetoxy-5-ethyl-sulphone-5α-cholestan-6-one oxime (CVII)

3β-Acetoxy-5-ethylmercapto-5α-cholestan-6-one oxime (LXXXVIIIa) (100 mg) in dichloromethane (10 mg) was treated with m-chloroperbenzoic acid (2 moles) at 0°C. The reaction mixture was ketp at room temperature for 20 min. After completion of the reaction the reaction mixture was worked up in usual manner and dried over anhydrous sodium sulphate. The solvent evaporation provided an amorphous solid (CVII) (80 mg).

Analysis Found : C, 67.57; H, 9.63; N, 2.51

$C_{31}H_{53}NO_5S$ requires : C, 67.51; H, 9.61; N, 2.54%.

IR : $\nu_{max.}$ 3440 (-OH), 1720 ($-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1640 (C=N), 1310, 1165 and 1125 ($-SO_2-$), 1230 and 1030 cm^{-1} (acetate).

^{1}H-NMR : δ 9.2 (br s, -OH, exchangeable with D_2O), 5.4 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H), 2.54 (m, $-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-CH_2-CH_3$), 2.0 (s, $-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1.25 (t, $-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-CH_2-CH_3$), 0.9 (C10β-$CH_3$), 0.66 (C13β-$CH_3$), 0.81 (other methyl protons).

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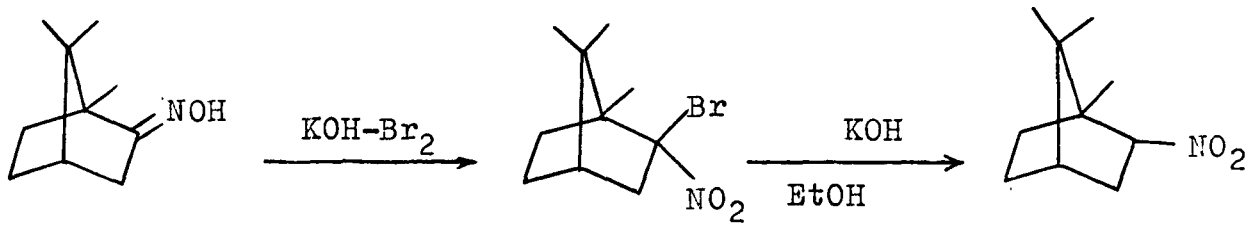
Part-Three

Oxidation of Steroidal Oximes

THEORETICAL

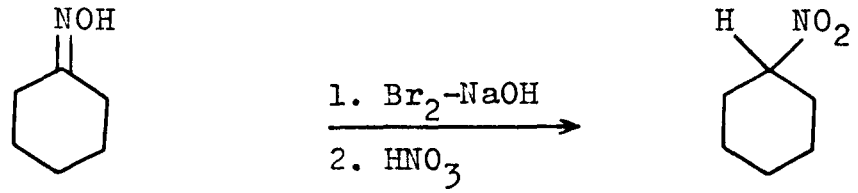
Oxidation of oximes to nitro compounds with peroxyfluoroacetic acid and other reagents have been utilized in order to prepare nitro compounds[1].

Foster[2] quantitatively prepared bromonitrocamphane (II) from camphor oxime (I) by treatment with KOH and bromine which was reduced with aqueous/alcoholic KOH to nitrocamphane (III) in 80% yield.



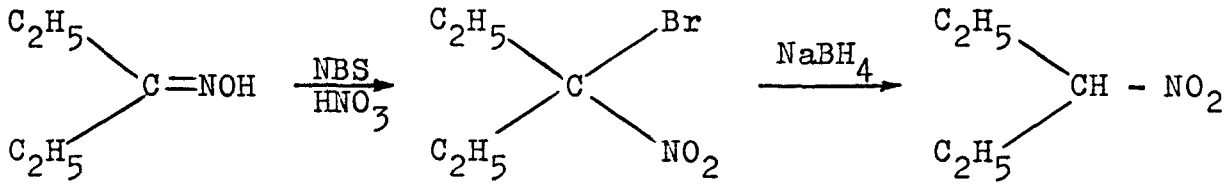
(I) (II) (III)

Iffland et al.[3] carried out the oxidation of cyclohexanone oxime (IV) to nitrocyclohexane (V) with Br_2-NaOH followed by treatment with HNO_3.



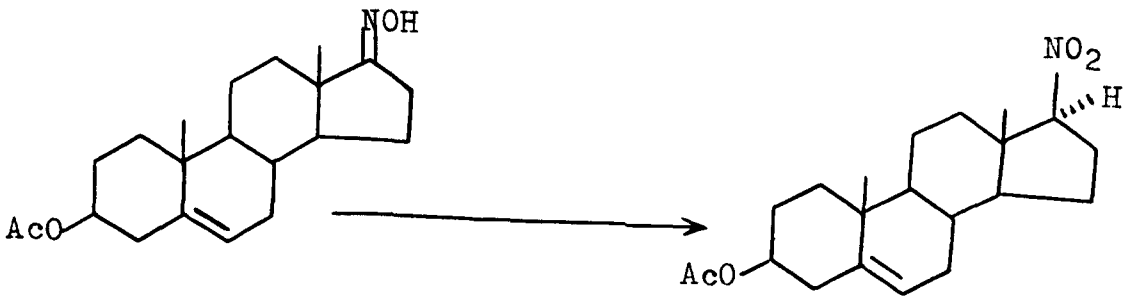
(IV) (V)

Iffland and Yen[4] extended the synthesis of nitro alkane (VIII) from oxime (VI) for the preparation of secondary nitroalkanes from aliphatic ketoximes.



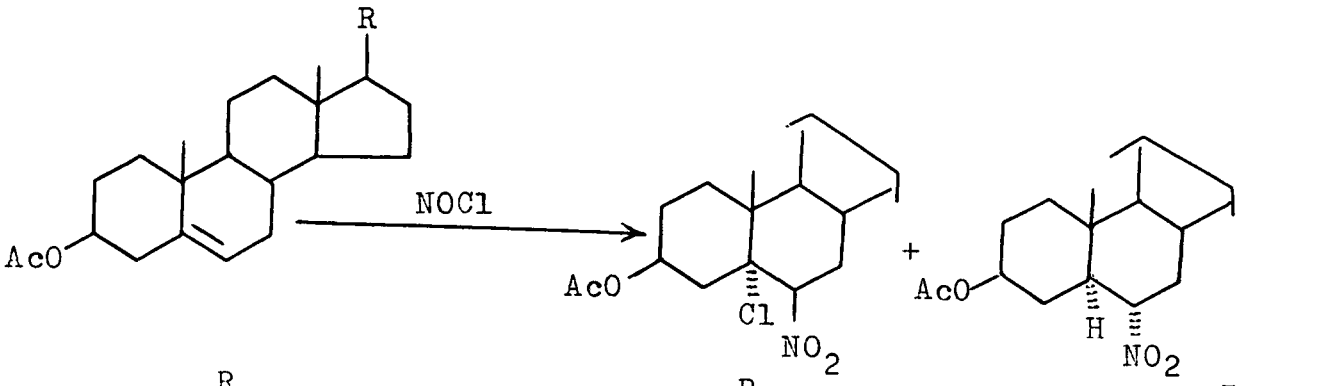
(VI) (VII) (VIII)

Patchett et al.[5] probed three methods for the synthesis of 17-nitrosteroids based on Iffland's oxidation of oximes[4], peracid oxidation of oximes and direct nitration[6,7]. The oxime of 3β-acetoxyandrost-5-en-17-one (IX) was reacted with N-bromosuccinimide in dioxan—aqueous potassium bicarbonate for two days and the entire crude was reduced by $NaBH_4$ to afford 3β-acetoxy-17-nitroandrost-5-ene (X) in 50-60% yield.



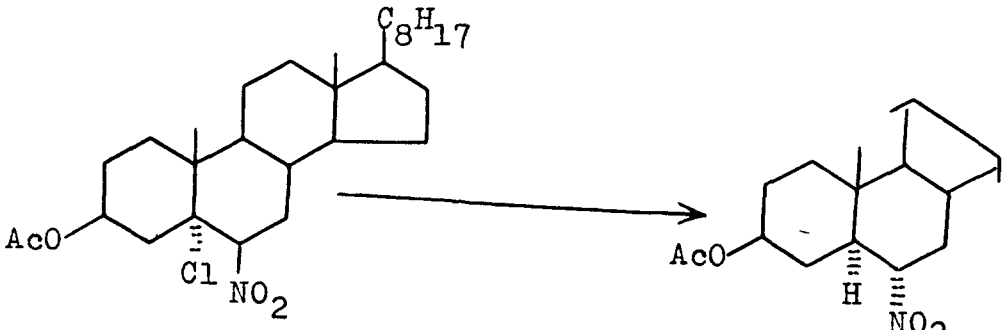
(IX) (X)

Tanabe and Hayashi[8] reported the preparation of α-chloro-nitro steroids by nitrocyl chloride. Cholesteryl acetate (XI) was reacted with excess of NOCl at $0^{o}C$ in dichloromethane or carbontetrachloride to give 3β-acetoxy-5α-chloro-6β-nitrocholestane (XII) and 3β-acetoxy-6α-nitro-5α-cholestane (XIII). Similar transformation was observed with 3β-acetoxyandrost —5-en-17-one (XIV).

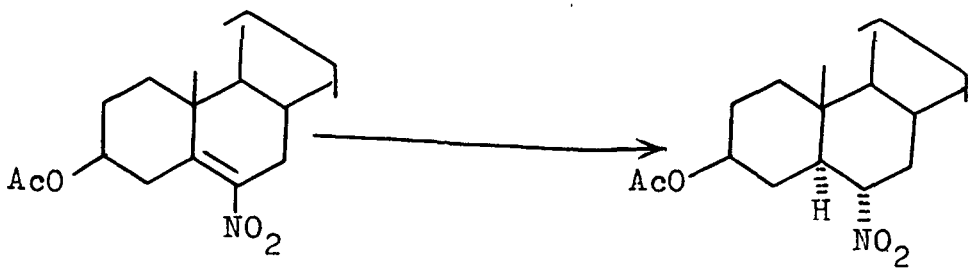


	R		R		R
(XI)	C_8H_{17}	(XII)	C_8H_{17}	(XIII)	C_8H_{17}
(XIV)	O	(XV)	O	(XVI)	O

Hassner and Heathcock[9] carried out the reduction of 3β-acetoxy-5α-chloro-6β-nitrocholestane (XVII) and 3β-acetoxy-6-nitrocholest-5-ene (XVIII) with $NaBH_4$ in ethyl alcohol to give 3β-acetoxy-6α-nitro-5α-cholestane (XIX).

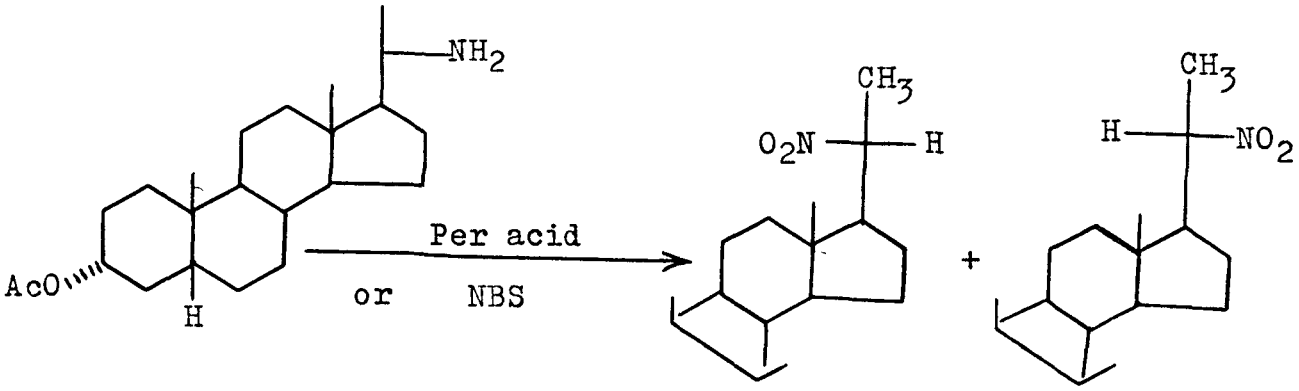


(XVII) (XIX)



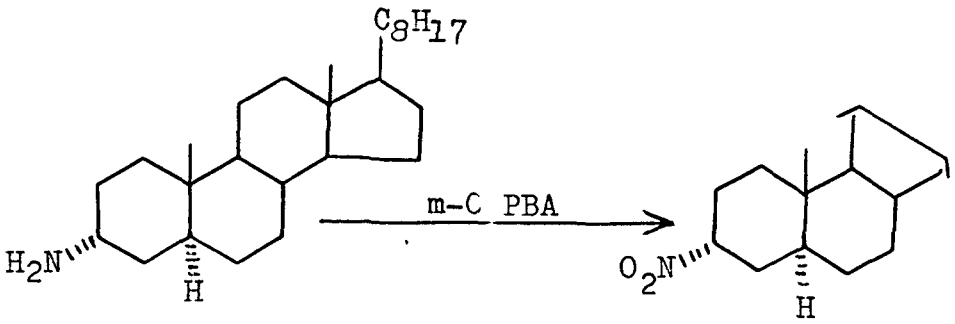
(XVIII) (XIX)

Robinson et al.[10] synthesized C20 nitrosteroids by conversion of C20 amine (XX) into the C20 nitro compounds (XXI and XXII) using peracid.



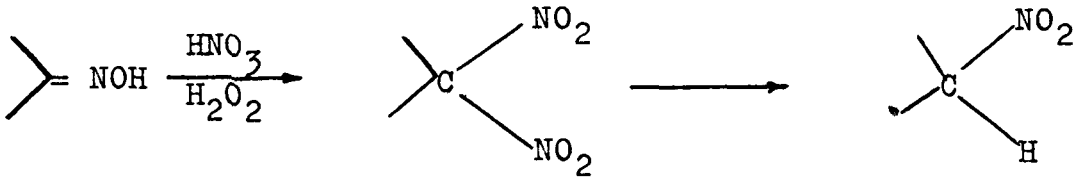
(XX) (XXI) (XXII)

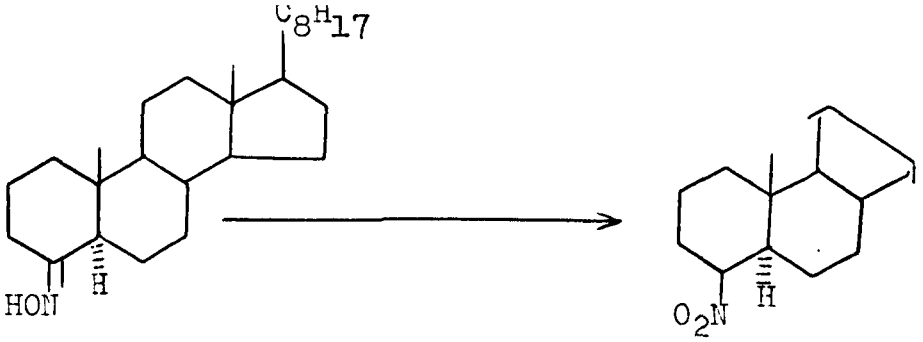
3α-Amino-5α-cholestane (XXIII) was oxidized with m-chloroperbenzoic acid to give 28% of 3α-nitro compound (XXIV)[10].



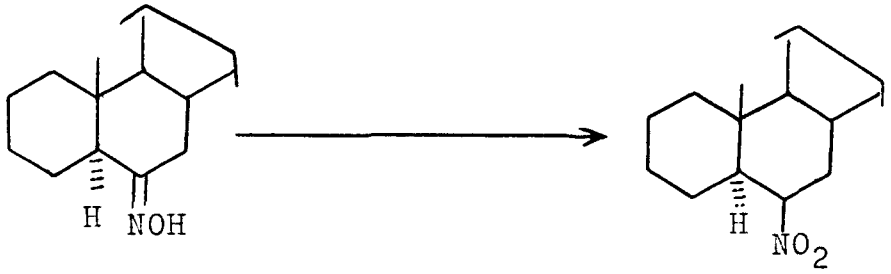
(XXIII) (XXIV)

Bull et al.[11] prepared gem-dinitro compounds by the reaction of fuming nitric acid and 30% H_2O_2 with oximes, which were hydrolysed to mononitro compounds. This procedure gave β-isomers at C4 and C6, α-isomer at C7 and a mixture of α-and β- isomers at C-3 of the steroids.





(XXV) (XXVI)

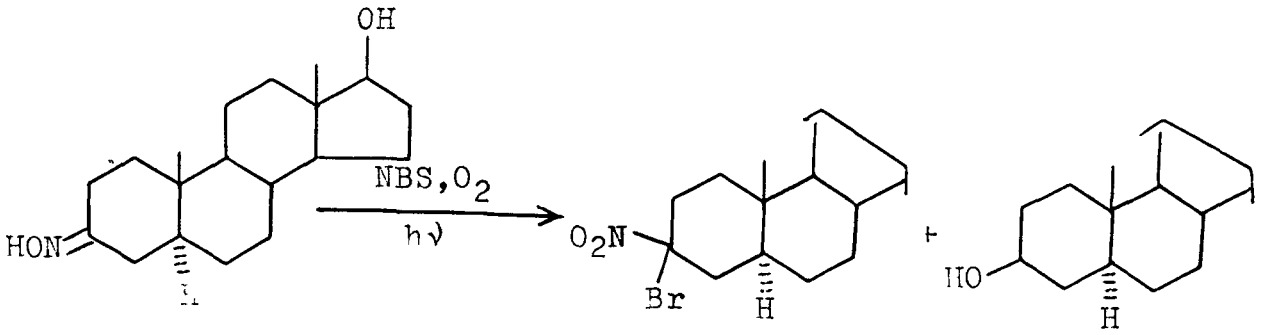


(XXVII) (XXVIII)

(XXIX) (XXX)

(XXXI) (XXXII)

Wolff and Boguslaski[12] treated 5α-androstan-17β-ol-3-one oxime (XXXIII) with N-bromosuccinimide in dioxan –water solution. The reaction mixture was stirred and exposed to air for 48 hrs and finally reduced with $NaBH_4$ to give a nitro compound (XXXIV), 27% and androstan-3β, 17β-diol (XXXV).



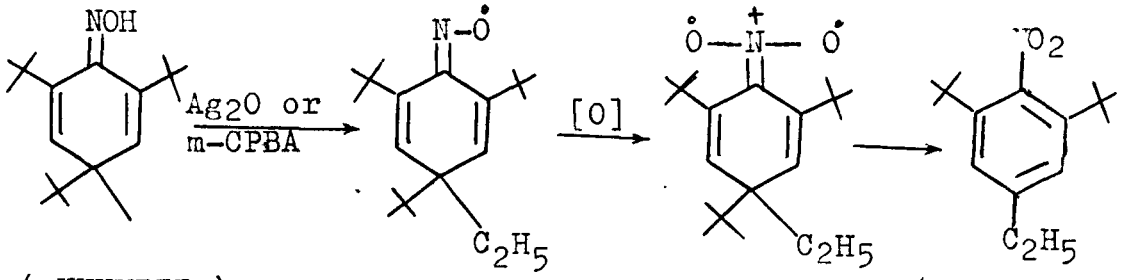
(XXXIII) (XXXIV) (XXXV)

Boyer and Frints[13] oxidized the amidoxime (XXXVI) into 1,2-diphenyl-2-nitrosoazomethine (XXXVII) with either $Pb(OAc)_4$, N-bromosuccinimide or diethylazodicarboxylate (DEAD).

$$C_6H_5 - \underset{\underset{NOH}{\|}}{C} - NH - C_6H_5 \xrightarrow[\text{NBS or DEAD}]{Pb(OAc)_4} C_6H_5 - \underset{\underset{NO}{|}}{C} = N - C_6H_5$$

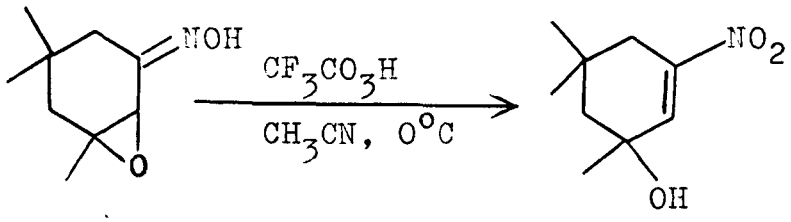
(XXXVI) (XXXVII)

Inagaki et al.[14] gave a preparative method for 4-alkyl-2,6-di-t-butylnitrobenzene (XXXIX) from oxidation of 4-alkyl-1-hydroximino-2,4,6-tri-t-butyl-2,5-cyclohexadiene (XXXVIII) with Ag_2O, m-chloroperbenzoic acid or nickel peroxide in benzene at room temperature in 96% yield.



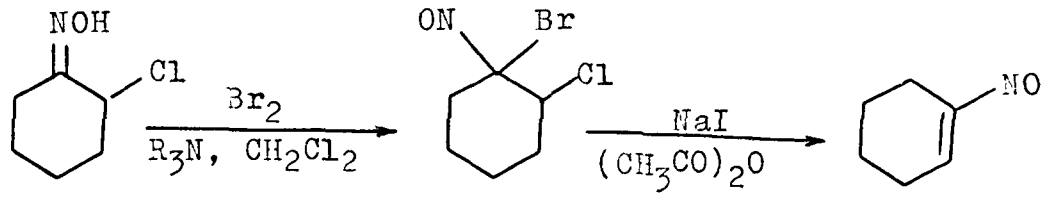
(XXXVIII) (XXXIX)

α,β-Epoxyoxime (XL) was oxidized to γ-hydroxy-α-nitro olefin (XLI) by trifluoroperoxyacetic acid by Tokamoto et al.[15].



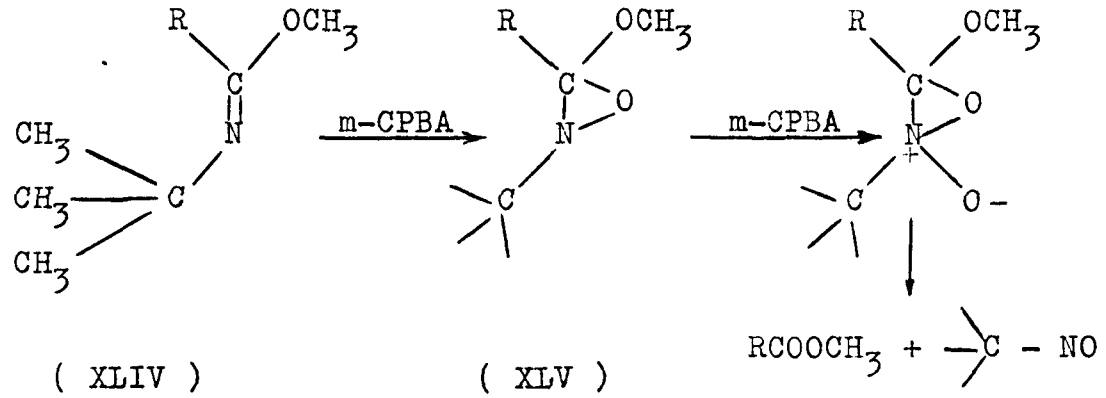
(XL) (XLI)

α-Chlorocyclohexanone oxime (XLII) when reacted with bromine in the presence of trialkylamine followed by treatment with sodium iodide in acetic anhydride provided nitroso cyclohex-1-ene (XLIII)[16].



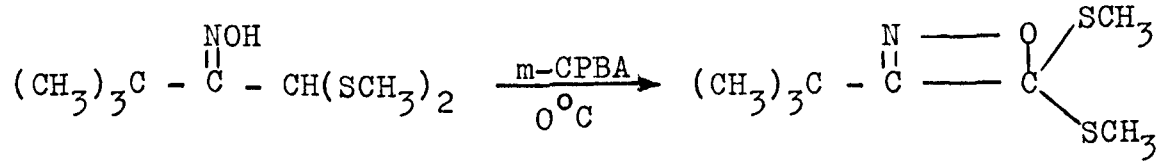
(XLII) (XLIII)

Acyclic imidate (XLIV) was oxidized by m-CPBA into oxaziridine (XLV) which was further oxidized to ester and a nitroso compound (XLVI)[17].



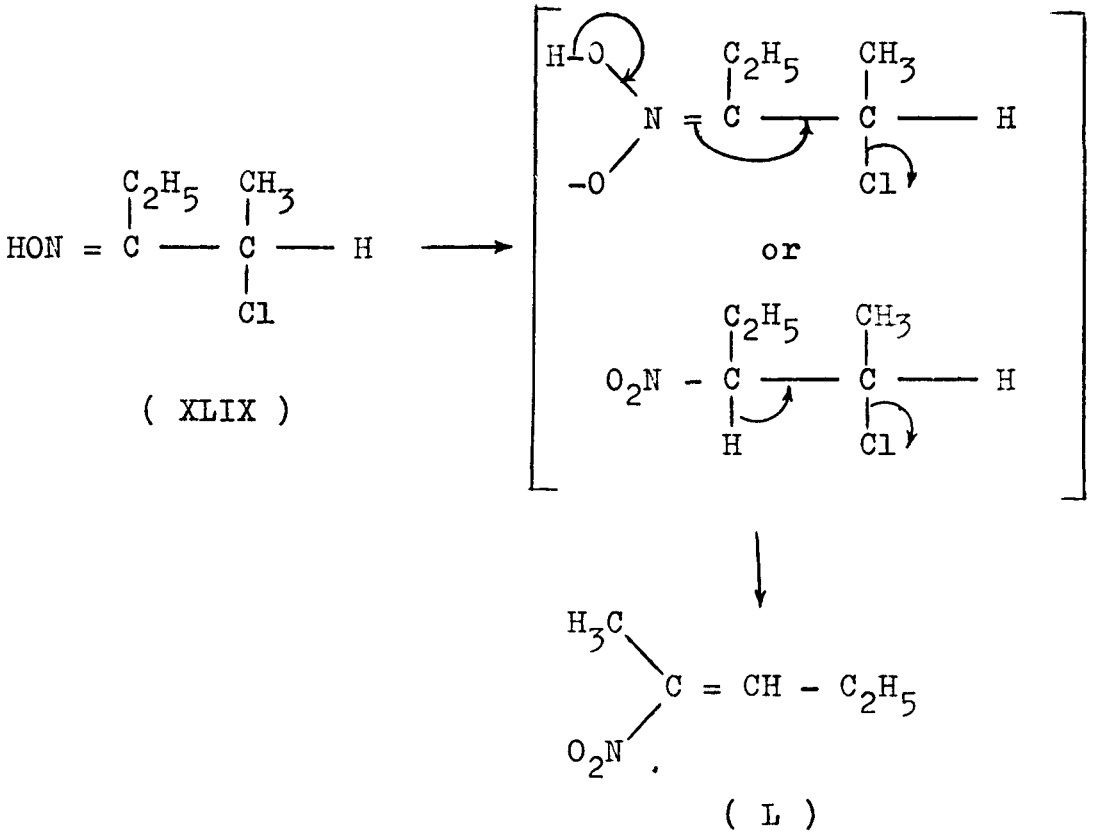
(XLIV) (XLV) (XLVI)

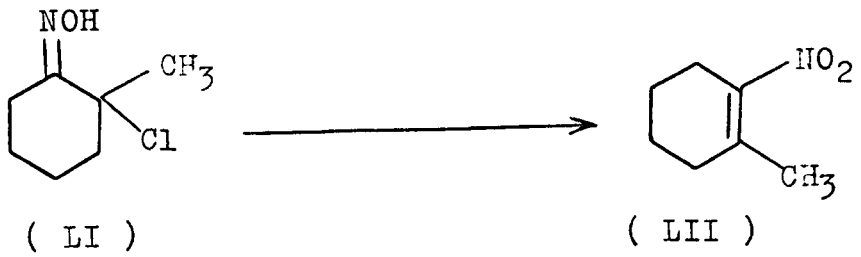
Corkins et al.[18] carried out the oxidation of (Z)-3,3-dimethyl-1,1-(dimethylthio)-2-butanone oxime (XLVII) with m-chloroperbenzoic acid in CH_2Cl_2 at 0°C which gave a 90% yield of 3-t-butyl-4,4-bis-(methylthio)-4H-1,2-oxazete (XLVIII).



(XLVII) (XLVIII)

Sudoh et al.[19] oxidized the oxime (XLIX) with trifluoroperacetic acid in acetonitrile in the presence of sodium hydrogen phosphate and urea[20], and obtained the corresponding α-nitro olefin (L) in morderate yield. Similar oxidation of 2-chloro-2-methylcyclohexanone oxime (LI) yielded 2-methyl-1-nitrocyclohexene (LII) in 40% yield.



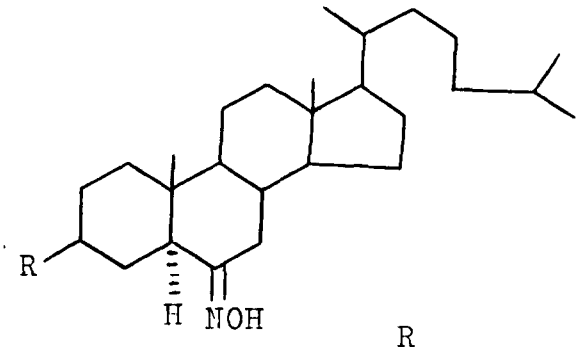


(LI) (LII)

DISCUSSION

A number of reagents have been reported to reduce nitro compounds, particularly in their aci forms, to oximes. Amongst these are alkaline solutions of sodium amalgum, zinc dust[21], sodium thiosulphate[22], and acidic hydrogen sulphide[23]. The carbonyl and nitro functional groups play a major role in organic syntheses[24]. The efficient conversion of one to the other, which enhances its utility, is readily accomplished in the nitro to carbonyl direction. However the conversion of carbonyl to nitro group, which is generally effected via oximes using very strong and nonselective oxidants (CF_3COOOH[20] and ozone[25] principally) is at present only narrowly applicable.

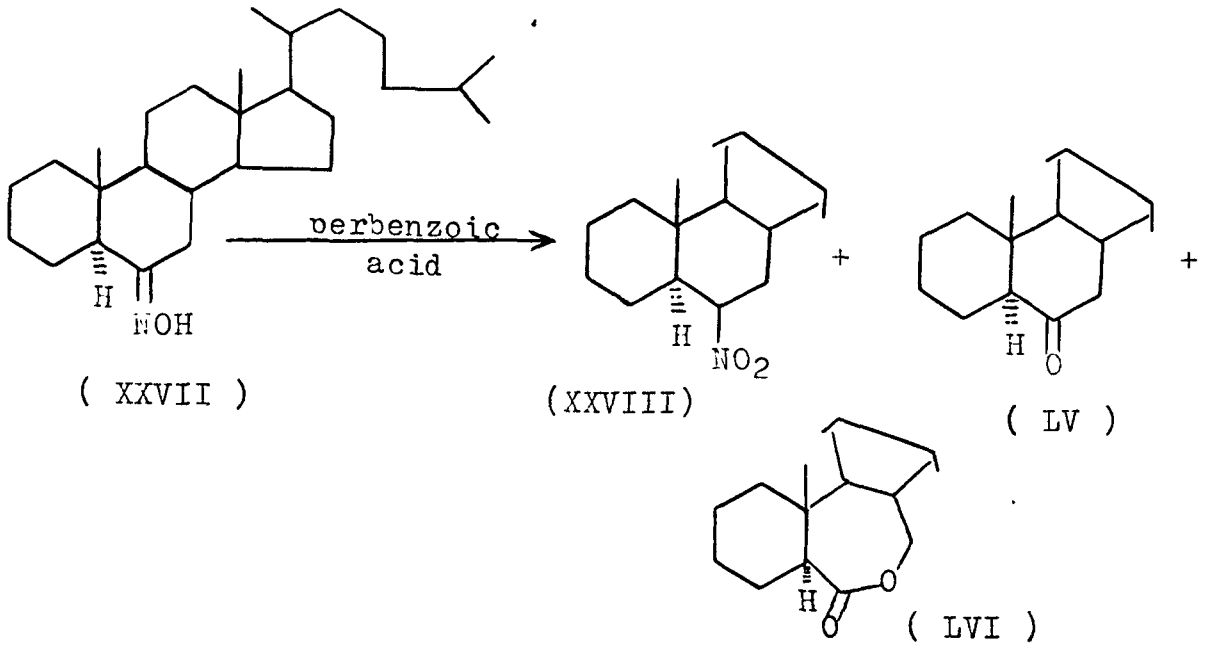
We have made an attempt to carry out the perbenzoic acid oxidation of some steroidal oximes such as 5α-cholestan-6-one oxime (XXVII), 3β-chloro-5α-cholestan-6-one oxime (LIII), and 3β-acetoxy-5α-cholestan-6-one oxime (LIV).



	R
(XXVII)	H
(LIII)	Cl
(LIV)	OAc

Reaction of 5α-cholestan-6-one oxime (XXVII) with perbenzoic acid

The oxime (XXVII) was treated with perbenzoic acid in chloroform at room temperature and the reaction mixture was kept at the same temperature for 24 hrs. After completion of the reaction, the reaction mixture was worked up in chloroform, and chromatographed over silica gel to provide compounds having m.p. 122°, 98° and 126° respectively.



(XXVII) (XXVIII) (LV) (LVI)

Characterization of the compound m.p. 122° as 6β-nitro-5α-cholestane (XXVIII)

The compound, m.p. 122° analysed correctly for $C_{27}H_{47}NO_2$. Its IR spectrum showed strong absorption bands at 1560 and 1390 cm^{-1} for nitro group. No other significant band was observed in the spectrum which clearly suggested that a nitro group has been introduced in the compound. The NMR spectrum of the compound exhibited a multiplet for one proton at δ 4.6 ($W\frac{1}{2}$ = 8 Hz, equatorial) for C6α-H. This signal, therefore, suggested that the orientation of nitro group is axial[9]. Methyl signals were seen at δ 0.93 (C10β-CH_3), 0.73 (C13β-CH_3) and 0.85 (other methyl protons). Thus on the basis of elemental analysis and spectral data, the compound, m.p. 122° was characterized as 6β-nitro-5α-cholestane (XXVIII).

Characterization of compound m.p. 98° as 5α-cholestan-6-one(LV)

The compound m.p. 98° analysed correctly for $C_{27}H_{46}O$ was found identical (mixed m.p., TLC, IR and NMR data) with the authentic sample of 5α-cholestan-6-one (LV) (reported[26] m.p. 95-96°).

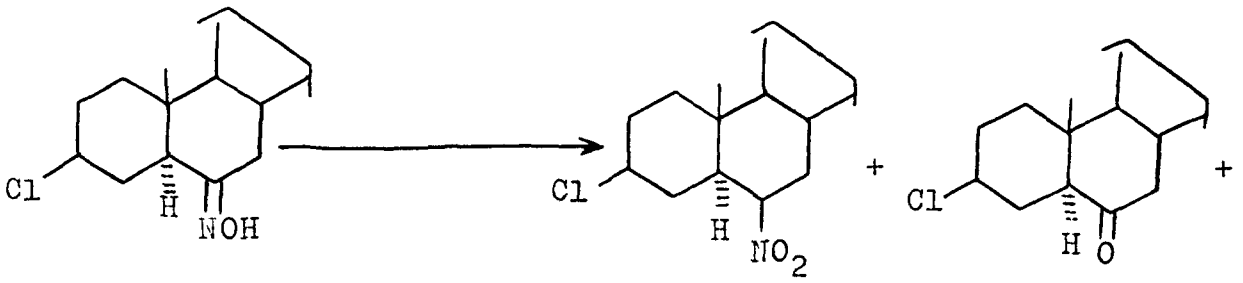
Characterization of the compound m.p. 126° as 7-oxa-B-homo-5α-cholestan-6-one (LVI)

The compound m.p. 126° analysed for $C_{27}H_{46}O_2$. Its IR spectrum showed the characteristic absorption band at 1720 cm^{-1}

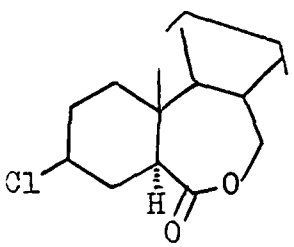
for ϵ-lactone[27]. Other important bands in the IR spectrum were at 1180, 1135 and 1080 cm^{-1} (C-O). The NMR spectrum displayed a broad singlet at δ 4.26 for C7a β-H, a doublet at 4.16 (J = 3.5 Hz) for (C7a α-H) and a double doublet at 2.65 ($J_{a,a}$ = 10 Hz; $J_{a,e}$ = 5 Hz) for C5α-H. Other signals were seen at δ 0.9 (C10β-CH_3), 0.7 (C13β-CH_3) and 0.8 (other methyl protons). These data suggested the structure of compound, m.p. 126° to be 7-oxa-B-homo-5α-cholestan-6-one (LVI).

Reaction of 3β-chloro-5α-cholestan-6-one oxime (LIII) with perbenzoic acid.

3β-Chloro-5α-cholestan-6-one oxime (LIII) was treated with perbenzoic acid in chloroform at room temperature for 24 hrs. Usual work up of reaction mixture in chloroform provided compounds m.p. 118°, 128-129° and 145°.



(LIII) (LVII) (LVIII)



(LIX)

Characterization of the compound m.p. 118° as 3β-chloro-6β-nitro-5α-cholestane (LVII)

The compound m.p. 118° analysed for $C_{27}H_{46}NO_2Cl$ (positive Beilstein test). The IR spectrum showed strong absorption bands at 1550 and 1380 cm^{-1} which were due to the presence of nitro group in the molecule. Its NMR spectrum exhibited two multiplets each integrating for one proton at δ 4.6 ($W\frac{1}{2}$ = 8 Hz; equatorial, C6α-H) and 3.6 ($W\frac{1}{2}$ = 17 Hz; axial; C3α-H)[28]. Methyl signals were observed at 0.96 (C10β-CH_3), 0.73 (C13β-CH_3), 0.86 and 0.80 (other methyl protons). These spectral data clearly suggested the structure of the compound m.p. 118° as 3β-chloro-6β-nitro-5α-cholestane (LVII).

Characterization of the compound m.p. 128-129° as 3β-chloro-5α-cholestan-6-one (LVIII)

The compound m.p. 128-129° (reported[29] m.p. 129°) was characterized as 3β-chloro-5α-cholestan-6-one (LVIII) on the basis of comparison of mixed m.p., TLC, IR, and NMR spectra with the authentic sample of 3β-chloro-5α-cholestan-6-one(LVIII).

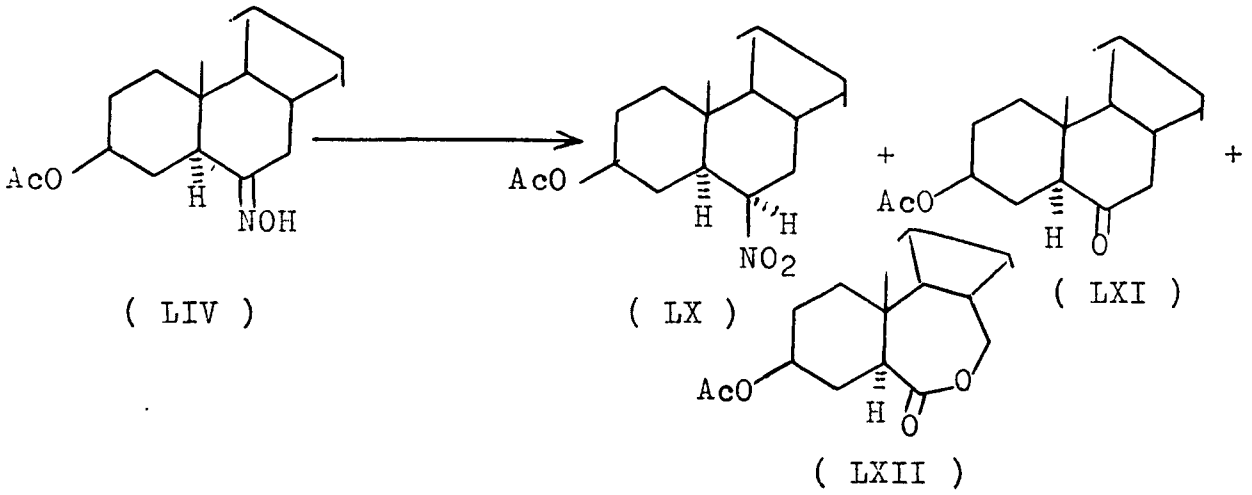
Characterization of the compound m.p. 145° as 3β-chloro-7-oxa-B-homo-5α-cholestan-6-one (LIX)

The compound m.p. 145° analysed for $C_{27}H_{45}O_2Cl$ (positive Beilstein test). Its IR spectrum showed characteristic band

at 1715 cm^{-1} for ϵ lactone[27]. Other IR bands were observed at 1195, 1130, 1085 (C-O) and 735 cm^{-1} (C-Cl). The NMR spectrum of the compound gave a broad singlet integrating for one proton at δ 4.09 for C7aβ-H, a doublet for one proton at δ 4.0 (J = 5 Hz; C7aα-H), one proton multiplet at 3.7 ($W\frac{1}{2}$ = 17 Hz; axial) for C3α-H and a double doublet for one proton at δ 2.85 ($J_{a,a}$ = 11 Hz; $J_{a,e}$ = 5 Hz) for C5α-H. Methyl signals were appeared at δ 0.9 (C10β-CH_3), 0.7 (C13β-CH_3) and 0.8 (other methyl protons). The foregoing discussion suggested the compound m.p. 145° to be 3β-chloro-7-oxa-B-homo-5α-cholestan-6-one (LIX).

Reaction of 3β-acetoxy-5α-cholestan-6-one oxime (LIV) with perbenzoic acid

3β-Acetoxy-5α-cholestan-6-one oxime (LIV) was dissolved in chloroform and treated with perbenzoic acid at room temperature for 24 hrs. After completion of the reaction, the reaction mixture was worked up in the usual manner and chromatographed over silica gel to afford compounds m.p. 153°, 127° and 181°.



(LIV) (LX) (LXI)

(LXII)

Characterization of the compound m.p. 153° as 3β-acetoxy-6β-nitro-5α-cholestane (LX)

The compound m.p. 153° analysed correctly for $C_{29}H_{49}NO_4$. The IR spectrum displayed absorption bands at 1730 ($-O\underline{C}O\underline{C}H_3$), 1560 and 1390 cm^{-1} (characteristic for $C-NO_2$ group). Its NMR spectrum gave two multiplets, integrating for one proton each at δ 4.7 ($W\frac{1}{2}$ = 8 Hz, equatorial)[9] for C6α-H and δ 4.6 ($W\frac{1}{2}$ = 18 Hz; axial) for C3α-H. A three proton singlet was observed at δ 2.1 for acetoxy protons. Methyl signals were appeared at δ 0.93 (C10β-$C\underline{H}_3$), 0.71 (C13β-$C\underline{H}_3$), 0.83 and 0.76 (other methyl protons). Thus these data suggested the structure of compound m.p. 153° to be 3β-acetoxy-6β-nitro-5α-cholestane (LX).

Characterization of the compound m.p. 127° as 3β-acetoxy-5α-cholestan-6-one (LXI)

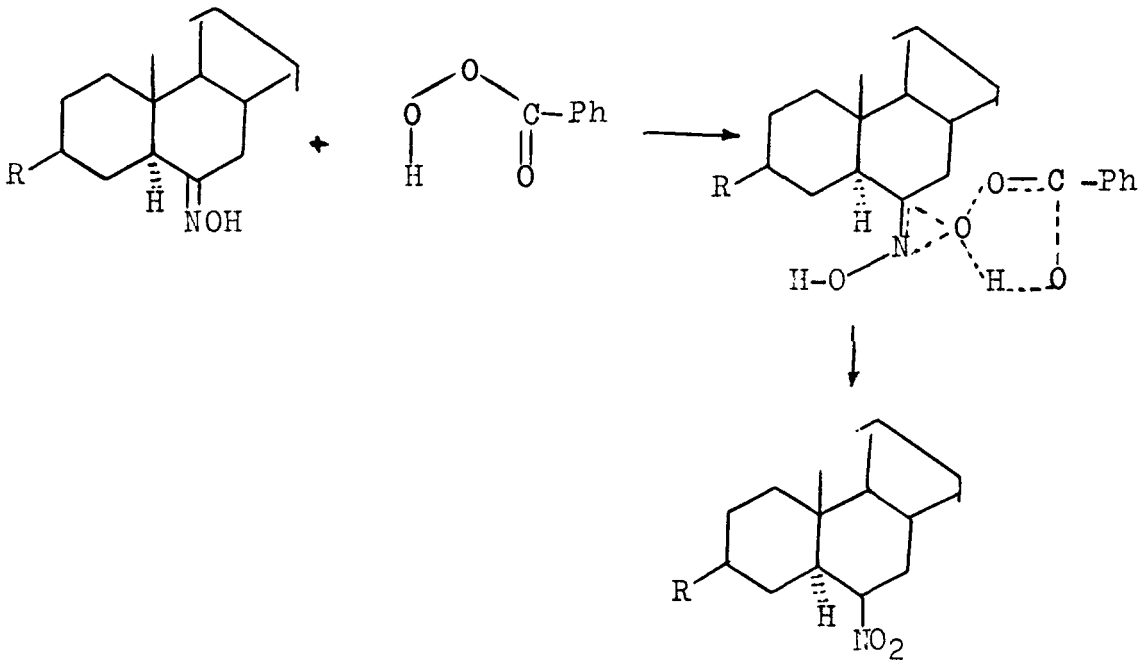
The compound m.p. 127° (reported[30] m.p. 128-29°) was characterized as 3β-acetoxy-5α-cholestan-6-one (LXI) on the

basis of the comparison of mixed m.p., TLC, IR and NMR spectra with the authentic sample prepared by the literature procedure.

Characterization of the compound m.p. 181° as 3β-acetoxy-7-oxa-B-homo-5α-cholestan-6-one (LXII)

The compound m.p. 181° analysed correctly for $C_{29}H_{48}O_4$. Its IR spectrum showed the characteristic absorption band at 1715 cm^{-1} for ϵ-lactone[27]. Other important bands were at 1740 ($-OCOCH_3$), 1205 and 1035 cm^{-1} (C-O). The NMR spectrum displayed one proton multiplet at δ 4.66 ($W\frac{1}{2}$ = 18 Hz; axial) for C3α-H, a broad singlet for C7aβ-H, at δ 4.1 a doublet at δ 4.0 (J = 3.5 Hz) for C7aα-H and a double doublet at 2.92 ($J_{a,a}$ = 11 Hz; $J_{a,e}$ = 5 Hz) which was ascribable for C5α-H). A three proton singlet was observed at δ 2.03 for acetoxy protons. Methyl signals were seen at δ 0.9, 0.8 and 0.7. The elemental analysis and spectral data of compound m.p. 181° suggested its structure as 3β-acetoxy-7-oxa-B-homo-5α-cholestan-6-one (LXII).

The formation of 6β-nitro compounds from their respective oximes can be explained on the basis of the following tentative mechanism.



Similar observations were made by Giguere and Olmos[31].

The 5α-cholestan-6-ones (LV , LVIII, LXI) were deoximation products which on oxidation with perbenzoic acid provided the lactones (LVI, LIX and LXII)[32].

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (IR) were determined in KBr with a Perkin-Elmer 237 spectrophotometer. IR values are given in cm^{-1}. Nuclear magnetic resonance spectra were run in $CDCl_3$ on a Varian A-60 instrument with tetramethylsilane (TMS) as the internal standard. The NMR values are given in ppm (δ). Thin layer chromatographic (TLC) plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate (Na_2SO_4) was used as drying agent. The abbreviations "s, d, t, m and br" denote "singlet, doublet, triplet, multiplet and broad' respectively.

Reaction of 5α-cholestan-6-one oxime (XXVII) with perbenzoic acid: 6β-Nitro-5α-cholestane (XXVIII), 5α-cholestan-6-one (LV) and 7-oxa-B-homo-5α-cholestàn-6-one (LVI)

5α-Cholestan-6-one oxime (XXVII) (2 g) was dissolved in chloroform (30 ml) and to this was added perbenzoic acid in chloroform (1.1 mole equivalent) at 0°C. The reaction mixture was kept at room temperature for 24 hrs. The reaction mixture was worked up in chloroform. The chloroform solution was washed successively with water, $NaHCO_3$ solution (5%), water and dried over anhydrous Na_2SO_4. Removal of the solvent

provided a residue which was chromatographed over silica gel (40 g) (each fraction of about 25 ml was collected). Elution with light petroleum-ether (20:1) gave (XXVIII), crystallized from light petroleum as needles (350 mg), m.p. 122°.

Analysis Found : C, 77.64; H, 11.20; N, 3.34

$C_{27}H_{47}NO_2$ requires : C, 77.69; H, 11.27; N, 3.35%.

IR : $\nu_{max.}$ 1560, 1390 cm^{-1} ($C-NO_2$).

^{1}H-NMR: δ 4.6 (m, $W\frac{1}{2}$ = 8 Hz, C6-α<u>H</u>), 0.93, 0.73 and 0.85 (C10β, C13β and other methyl protons).

Further elution with light petroleum-ether (18:1) afforded ketone (LV) (500 mg), m.p. and m.m.p. 96-98°[26]. Elution with light petroleum-ether (10:1) provided lactone (LVI), crystallized from light petroleum as white crystals (380 mg), m.p. 126°.

Analysis Found : C, 80.53; H, 11.40,

$C_{27}H_{46}O_2$ requires : C, 80.59; H, 11.42%.

IR : $\nu_{max.}$ 1720 (lactone), 1180, 1135 and 1080 cm^{-1}(C-O).

^{1}H-NMR : δ 4.26 (br s, C7a-β<u>H</u>), 4.16 (d, J = 3.5 Hz, C7a-α<u>H</u>), 2.65 (dd, $J_{a,a}$ = 10 Hz, $J_{a,e}$ = 5 Hz, C5-α<u>H</u>), 0.9, 0.8 and 0.7 (C10β, C13β and other methyl protons).

<u>Reaction of 3β-chloro-5α-cholestan-6-one oxime (LIII) with perbenzoic acid: 3β-Chloro-6β-nitro-5α-cholestane (LVII), 3β-chloro-5α-cholestan-6-one (LVIII) and 3β-chloro-7-oxa-B-homo-5α-cholestan-6-one (LIX)</u>

A solution of 3β-chloro-5α-cholestan-6-one oxime (LIII)

(2.0 g) in chloroform was added perbenzoic acid in chloroform (1.1 mole equivalent) at 0° and was kept at room temperature for 24 hrs. The reaction was worked up in usual manner and dried over anhydrous sodium sulphate. The solvent evaporation provided a semisolid which was column chromatographed over silica gel (40.0 g). Elution with light petroleum and ether (20:1) afforded (LVII), crystallized from light petroleum as shining crystals (340 mg), m.p. 118°.

Analysis Found : C, 72.63; H, 10.31; N, 3.07

$C_{27}H_{46}NO_2Cl$ requires : C, 71.68; H, 10.39; N, 3.09%.

IR : $\nu_{max.}$ 1550 and 1380 (C-NO_2), 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 4.6 (m, $W\frac{1}{2}$ = 8 Hz, C6-α$\underline{H}$), 3.6 (m, $W\frac{1}{2}$ = 17 Hz, C3-α$\underline{H}$), 0.96, 0.73, 0.86 and 0.80 (C10β, C13β and other methyl protons).

Further elution with light petroleum-ether (15:1) gave ketone (LVIII) (440 mg), m.p. and m.m.p. 128-129°)[29]. Elution with petroleum-ether (4:1) provide lactone (LIX), crystallized from light petroleum as white crystals (390 mg), m.p. 145°.

Analysis Found : C, 73.29; H, 10.30;

$C_{27}H_{45}O_2Cl$ requires : C, 74.31; H, 10.32%.

IR : $\nu_{max.}$ 1715 (lactone), 1195, 1130, 1085 (C-O) and 735 cm^{-1} (C-Cl).

^{1}H-NMR : δ 4.09 (br s, C7aβ-$\underline{H}$), 4.0 (d, J = 5 Hz, C7a-α$\underline{H}$), 3.7 (m, $W\frac{1}{2}$ = 17 Hz, C3-α$\underline{H}$), 2.85 (dd, $J_{a,a}$ = 11 Hz, $J_{a,e}$ = 5 Hz, C5-α$\underline{H}$), 0.9, 0.8 and 0.7 (C10β, C13β and other methyl protons).

Reaction of 3β-acetoxy-5α-cholestan-6-one oxime (LIV) with perbenzoic acid: 3β-Acetoxy-6β-nitro-5α-cholestane (IX), 3β-acetoxy-5α-cholestan-6-one (LXI) and 3β-acetoxy-7-oxa-B-homo-5α-cholestan-6-one (LXII)

3β-Acetoxy-5α-cholestan-6-one oxime (LIV) (2.0 g) was treated with perbenzoic acid in chloroform (1.1 mole equiv.) as described earlier. The reaction mixture was worked up in usual manner and dried over anhydrous sodium sulphate and column chromatographed over silica gel (40 g). Elution with light petroleum-ether (20:1) afforded LX, crystallized from light petroleum as shining crystals (380 mg), m.p. 153°.

Analysis Found : C, 73.27; H, 10.33; N, 2.96

$C_{29}H_{49}NO_4$ requires : C, 73.26; H, 10.31; N, 2.94%.

IR : $\nu_{max.}$ 1730 ($-O\underline{C}OCH_3$), 1560 and 1390 ($C-NO_2$), 1240, 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 4.7 (m, $W\frac{1}{2}$ = 8 Hz, C6-α$\underline{H}$), 4.6 (m, $W\frac{1}{2}$ = 18 Hz, C3α-$\underline{H}$), 2.1 (s, $-OCO\underline{CH}_3$), 0.93, 0.71, 0.83 and 0.76 (C10β, C13β and other methyl protons).

Further elution with light petroleum-ether (18:1) gave the ketone (LXI) (470 mg), m.p. and m.m.p.[30] 127°. Further elution with light petroleum and ether (7:1) afforded LXII, crystallized from light petroleum as white shining crystals (330 mg), m.p. 181°.

Analysis Found : C, 75.68; H, 10.45

$C_{29}H_{48}O_4$ requires : C, 75.65; H, 10.43%.

IR : $\nu_{max.}$ 1740 (-OCOCH$_3$), 1715 (lactone), 1205, 1035 cm^{-1} (acetate, C-O).

^{1}H-NMR : δ 4.66 (m, $W_{\frac{1}{2}}$ = 18 Hz, C3-αH), 4.1 (br s, C7a-βH), 4.0 (d, J = 3.5 Hz, C7a-αH), 2.92 (dd, $J_{a,a}$ = 11 Hz; $J_{a,e}$ = 5 Hz, C5-αH), 2.03 (s, OCOCH$_3$), 6.9, 0.8 and 0.7 (C10β and C13β and other methyl protons).

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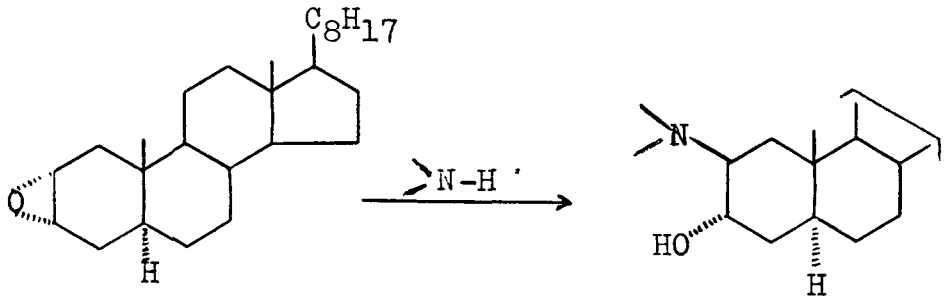
Part-Four

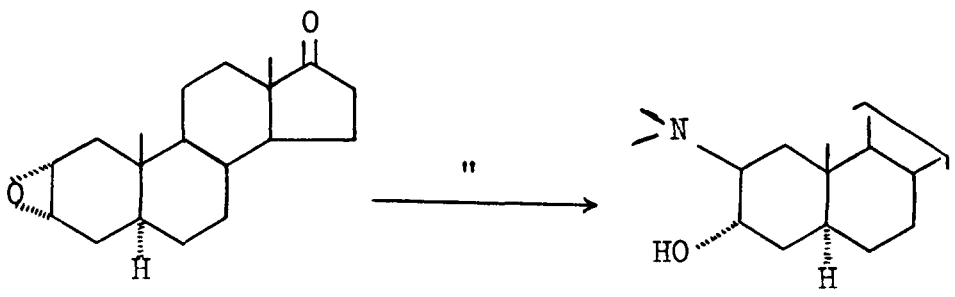
Preparation of Aminosterols

THEORETICAL

In 1961 Svoboda et al.[1] first reported the preparation of amino alcohols from steroidal epoxides. They carried out the condensation of 2α,3α-epoxy-5α-cholestane (I) with dimethylamine in order to obtain 2β-dimethylamino-5α-cholestan-3α-ol (II). A similar synthesis of 2β-dimethylamino-3α-hydroxy-5α-androstan-17-one (IV) from 2α,3α-epoxy-5α-androstan-17-one (III) has been reported.

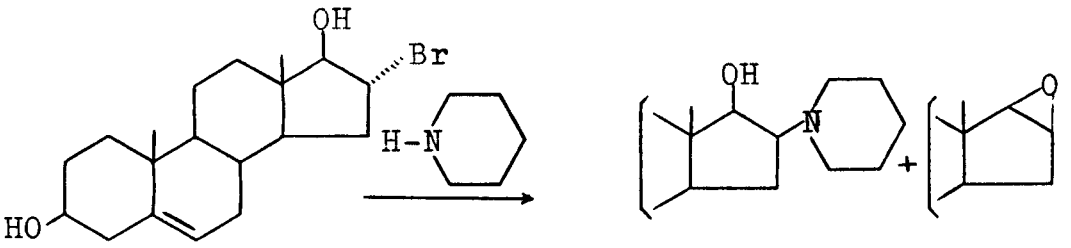


(I) (II)



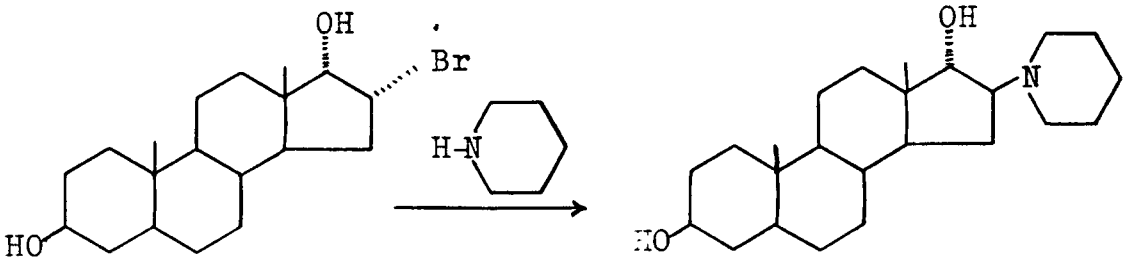
(III) (IV)

Hewett and Savage[2] carried out the condensation of 16α-bromoandrost-5-ene-3β,17β-diol (V) with piperidine which afforded 16β-piperidino-17β-alcohol (VI) along with 16β,17β-epoxide (VII).



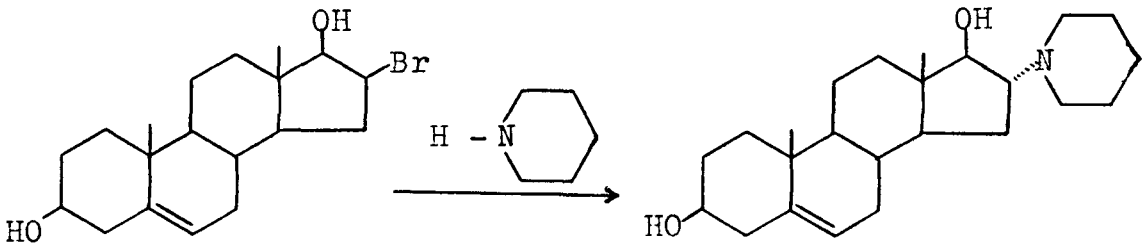
(V) (VI) (VII)

Similar condensation of 16α-bromo-17α-ol (VIII) with piperidine gave 16β-piperidino-17α-ol (IX) in 6% yield.



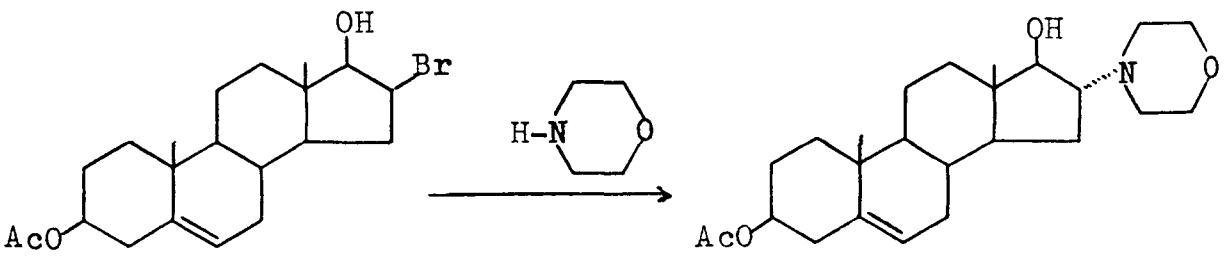
(VIII) (IX)

Under similar reaction conditions the 16β-bromo-17β-ol (X) gave 43% of 16α-piperidino-17β-ol (XI), indicating that bromohydrin (X) is more readily attacked on α-face of the molecule than the bromohydrin (VIII) attacked on β-face.

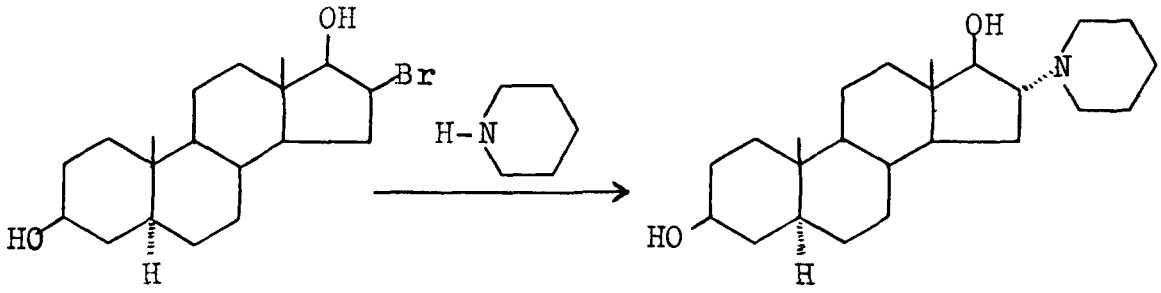


(X) (XI)

Condensation of 3β-acetoxy-16β-bromoandrost-5-en-17β-ol (XII) with morpholine gave 3β-acetoxy-16α-morpholinoandrost-5-en-17β-ol (XIII). Similar condensation of 16β-bromo-5α-androstane-3β, 17β-diol (XIV) with piperidine followed by hydrolysis of the product, gave 16α-piperidino-5α-androstane-3β,17β-diol (XV).

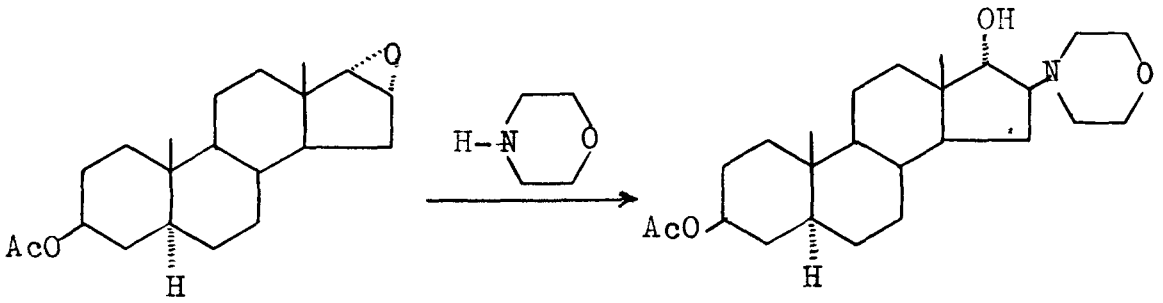


(XII) (XIII)



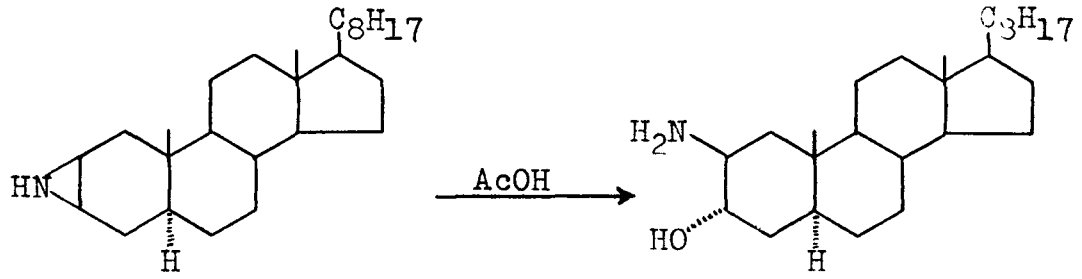
(XIV) (XV)

Condensation of 3β-acetoxy-16α,17α-epoxy-5α-abdrostane (XVI) with morpholine like wise furnished a trans isomer 3β-acetoxy-16β-morpholino-5α-androstan-17α-ol (XVII).



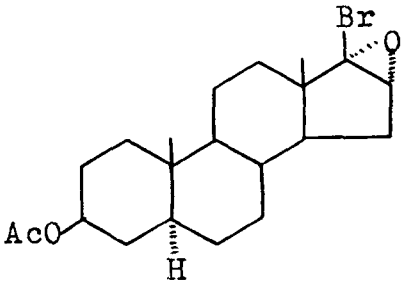
(XVI) (XVII)

Hassner and Heathcock[3] prepared aminoalcohols via transdiaxial[4] ring opening of aziridines. 2β,3β-Iminocholestane (XVIII) was treated with acetic acid to give 2β-amino-3α-hydroxy-5α-cholestane (XIX) in 90% yield.

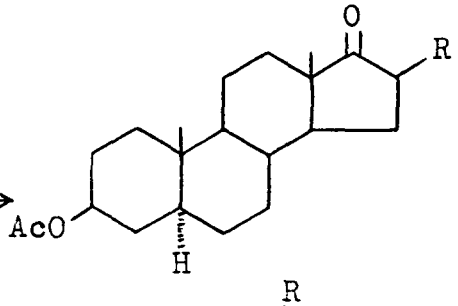


(XVIII) (XIX)

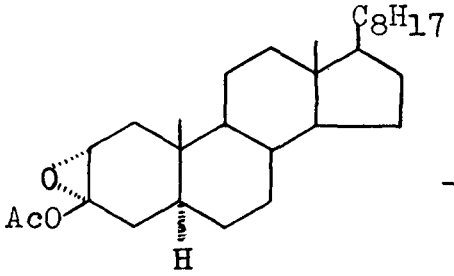
Hassner and Catsoulacos[5] treated steroidal epoxides with primary or secondary amines at room temperature to obtain amino ketones. 3β-Acetoxy-16α,17α-oxido-17β-bromo-5α-androstane (XX), for example was reacted with isopropylamine, diethylamine and morpholine to give amino ketones (XXI-XXIII), respectively. When 3β-acetoxy-2α,3α-oxidocholestane (XXIV) was treated with piperidine, morpholine or 2,6-dimethylmorpholine ketones (XXV-XXVII), were obtained. Reduction of the ketosteroids (XXV-XXVII) with sodium borohydride afforded amino alcohols (XXVIII-XXX).



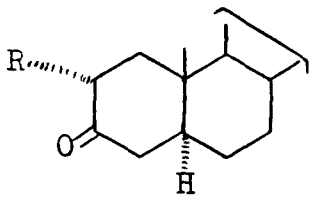
(XX)

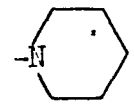
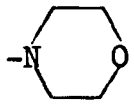
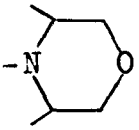


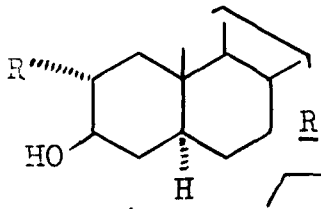
	R
(XXI)	$NHCH(CH_3)_2$
(XXII)	$N(C_2H_5)_2$
(XXIII)	$N(CH_2)_4CH_2$

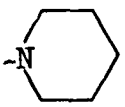
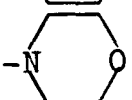
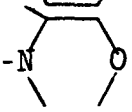


(XXIV)

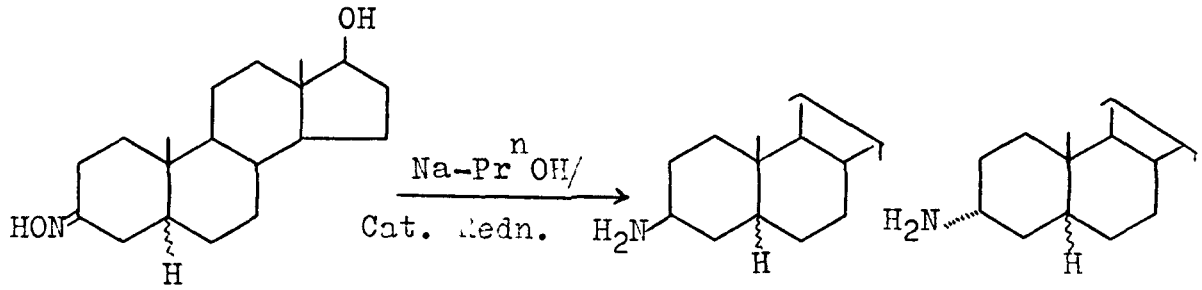


	R
(XXV)	
(XXVI)	
(XXVII)	



	R
(XXVIII)	
(XXIX)	
(XXX)	

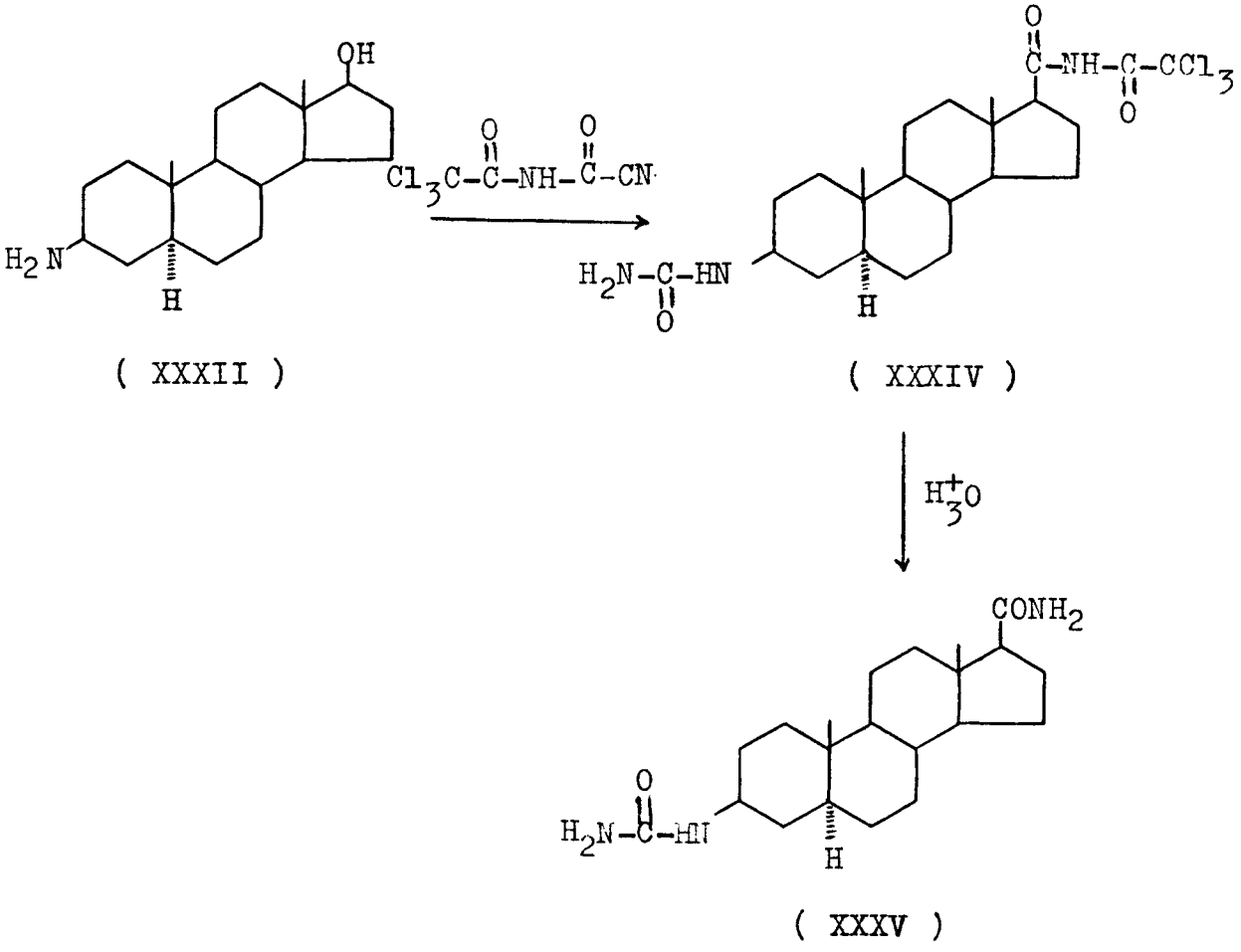
The synthesis of 3β-amino-5α-androstan-17β-ol (XXXII) and its 3α-amino epimer (XXXIII) from 3-oximino-5α-androstan-17β-ol (XXXI) has been reported[6,7]. Yagi et al.[8] treated 3-oximino-5β-androstan-17β-ol (XXXIa) with sodium and n-propyl alcohol to afford the equatorial 3α-amino-5β-androstan-17β-ol (XXXIIIa) in good yield while catalytic reduction of the oxime yielded the axial 3β-amino-5β-androstan-17β-ol (XXXIIa).



(XXXI) 5α-H (XXXII) 5α-H (XXXIII) 5α-H

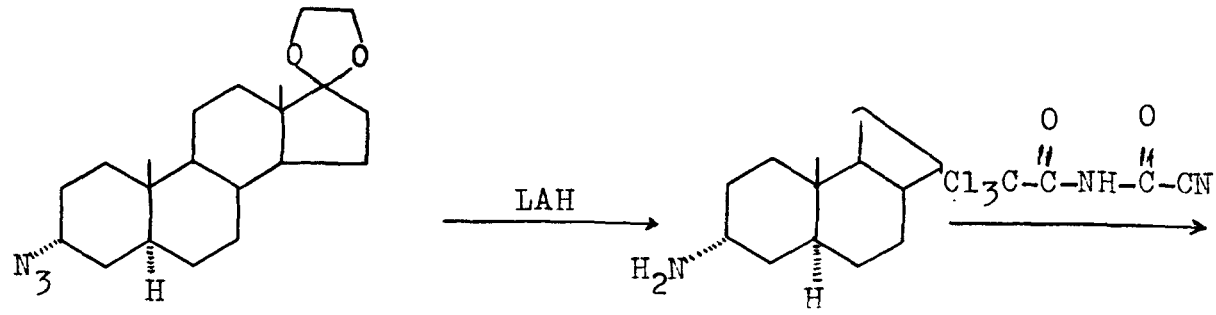
(XXXIa) 5β-H (XXXIIb) 5β-H (XXXIIIa) 5β-H

Treatment of 3β-amino-5α-androstan-17β-ol (XXXII) with trichloroacetoisocyanate gave 3β-(N-trichloroacetylureido)-5α-androstan-17β-yl N-trichloroacetylcarbamate (XXXIV) which was hydrolysed with acid to 3β-ureido-5α-androstan-17β-yl carbamate (XXXV). The overall yield from free base was 50-70%[8].

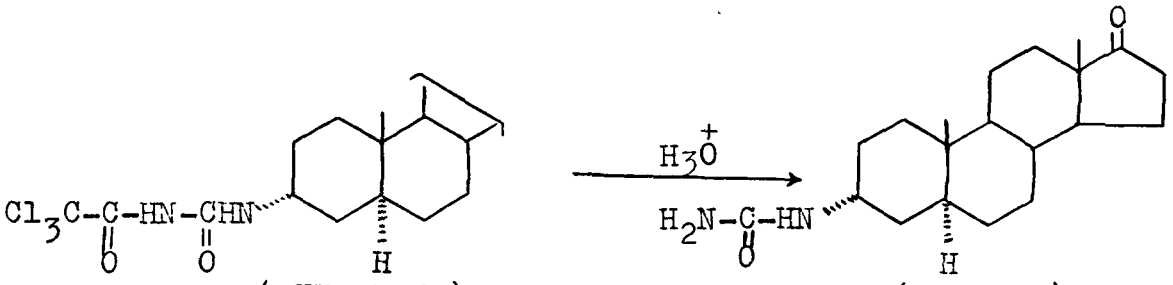


(XXXII) (XXXIV) (XXXV)

An alternate synthesis of 3α-ureido-5α-androstan-17-one (XXXIX) was also explored[8]. The ethylene ketal of 3α-azido-5α-androstan-17-one (XXXVI) was prepared and the product was reduced with $LiAlH_4$ to yield 3α-amino-5α-androstan-17-one-ketal (XXXVII), isolated as acetate salt. The salt was then treated with trichloroacetoisocyanate and the resulting trichloroacetylureido derivative (XXXVIII) was hydrolysed with acid and 3α-ureido-5α-androstan-17-one (XXXIX) was obtained in about 30% yield from (XXXVI).

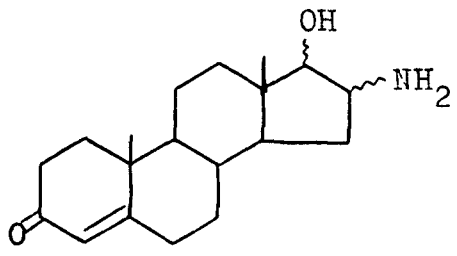


(XXXVI) (XXXVII)

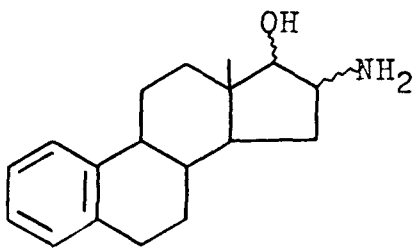


(XXXVIII) (XXXIX)

Overbeek and Bonta[9] prepared 16-amino-17-hydroxy-androstane (XL) and 16-amino-17-hydroxy-oestra-1,3,5(10)-triene (XLa) which were found to possess tranquilizing and anticonvulsant activities.

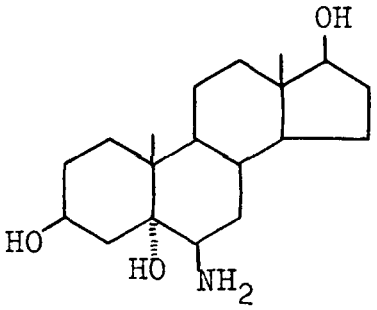


(XL)

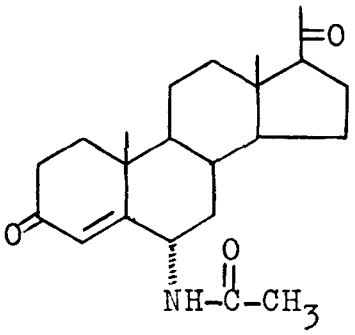


(XLa)

Several workers have reported[10-14] 6-aminosteroids, two of which, 6β-aminoandrostane-3β,5α,17β-triol (XLI) and 6α-acetamidoprogesterone (XLII) have anaesthetic properties[10].



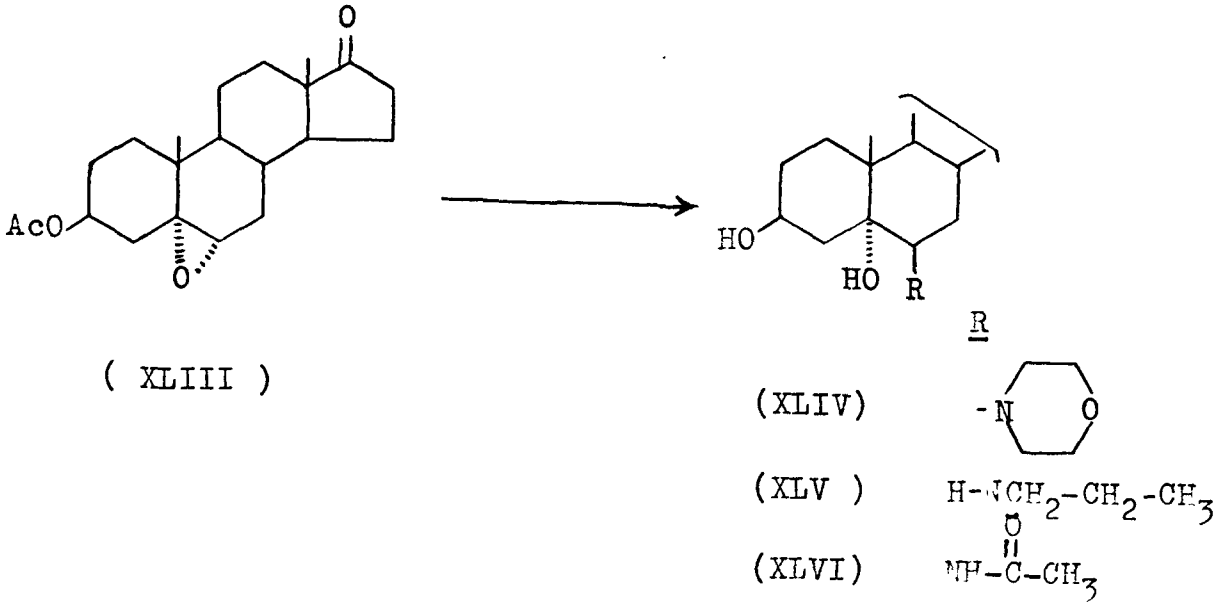
(XLI)



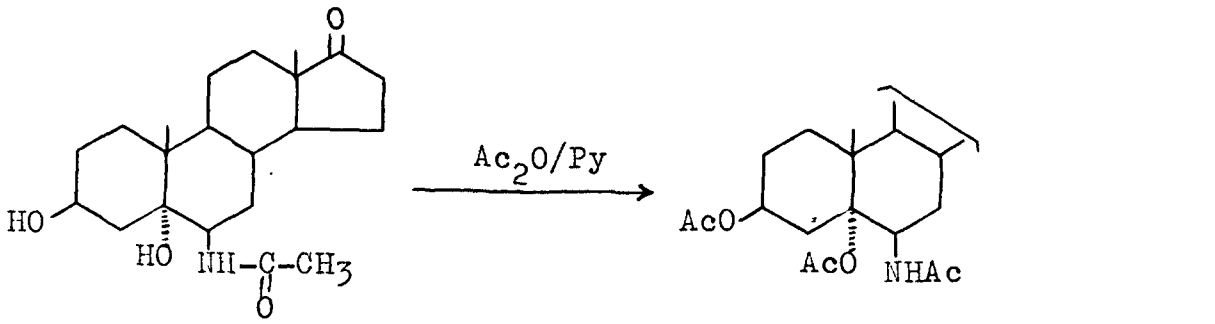
(XLII)

Hewett and Savage[15] reported the preparation of several amino steroids. 6β-Amino-5α-hydroxy steroids were prepared by cleaving the coresponding 5α,6α-epoxides with ammonia or a primary or secondary amine at temperatures varying from 80° to 120° in the presence of water. 3β-Acetoxy-5α,6α-epoxyandrostan-17-one (XLIII) was completely cleaved in three days by boiling with morpholine containing 10% water to give 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (XLIV). The condensation of the epoxide with boiling n-propylamine with 10% water or with ammonia in methanol and subsequent alkaline hydrolysis yielded 3β,5α-dihydroxy-6β-propylaminoandrostan-17-one (XLV). However, when epoxide (XLIII) was condensed with a solution of ammonia in aqueous dioxan 6β-acetamido-3β,5α-dihydroxyandrostan-17-one (XLVI)

was obtained. Acetylation of (XLVI) gave the diacetate (XLVII).

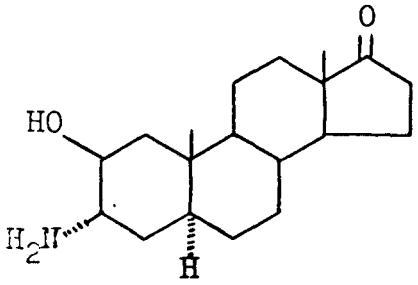


(XLIII)



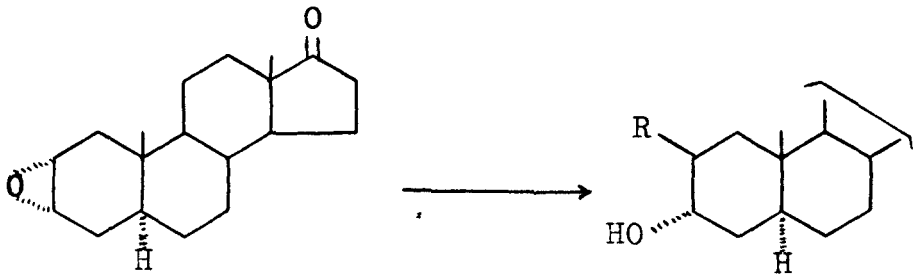
(XLVI) (XLVII)

Hewett and Savage[16] gave the synthesis of 3α-amino-2β-hydroxy-5α-androstan-17-one (XLVIII), the hydrochloride of which was found to be novel anti-arrythmic drug[16].

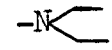
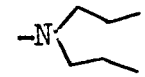
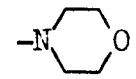
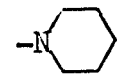
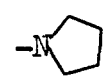


(XLVIII)

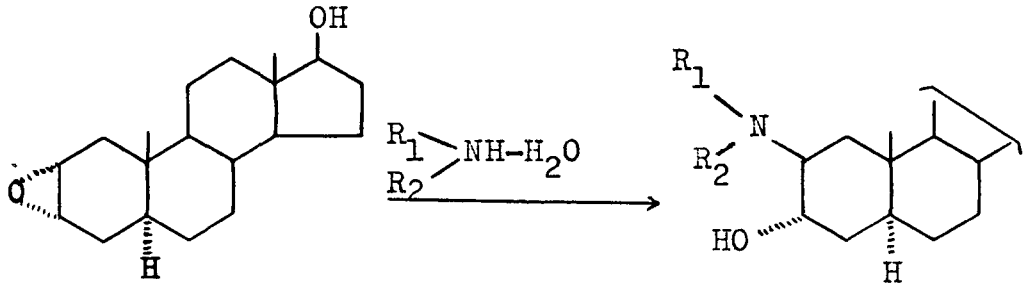
Condensation of 2α,3α-epoxy-5α-androstan-17-one (III) with primary or secondary amine in the presence of water gave the corresponding 2β-amino-3α-hydroxy-5α-androstan-17-one (XLIX-LV). These reactions were catalysed by water possibly by the formation of the more reactive intermediate oxomium ion[16].



(III)

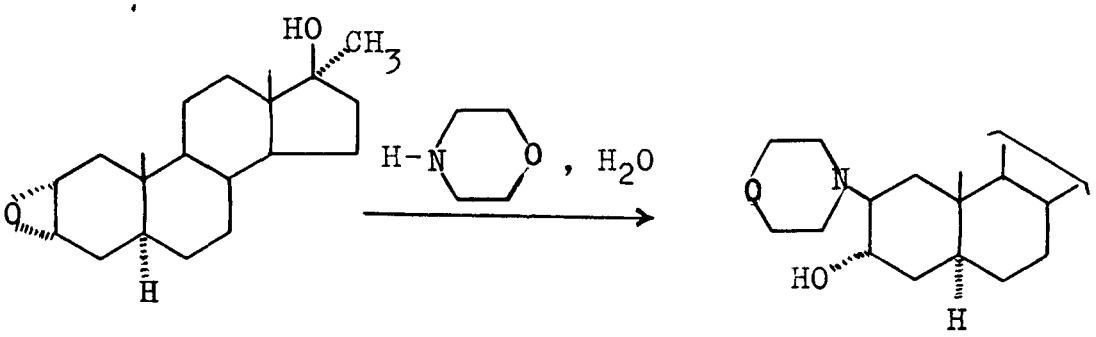
	R
(XLIX)	-NH-CH_3
(L)	
(LI)	
(LII)	
(LIII)	
(LIV)	
(LV)	

The condensation of 2α,3α-epoxy-5α-cholestan-17β-ol (LVI) with secondary amine in water gave the corresponding 2β-amino-5α-androstane-3α,17β-diol[16] (LVII).



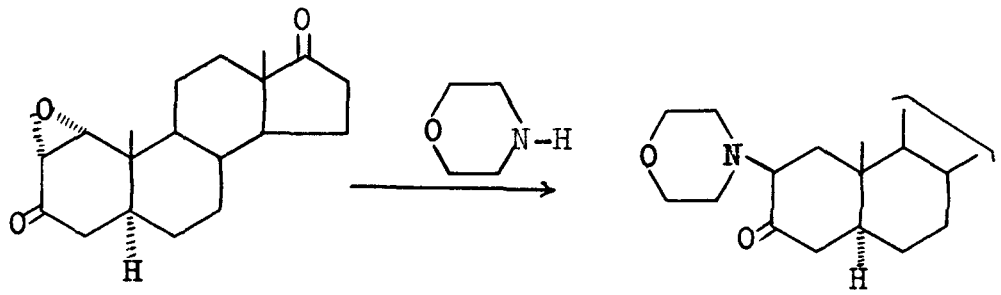
(LVI) (LVII)

Condensation of 2α,3α-epoxy-17α-methyl-5α-androstan-17β-ol (LVIII) with aqueous morpholine gave 17α-methyl-2β-morpholino-5α-androstane-3α,17β-diol (LIX)[16].



(LVIII) (LIX)

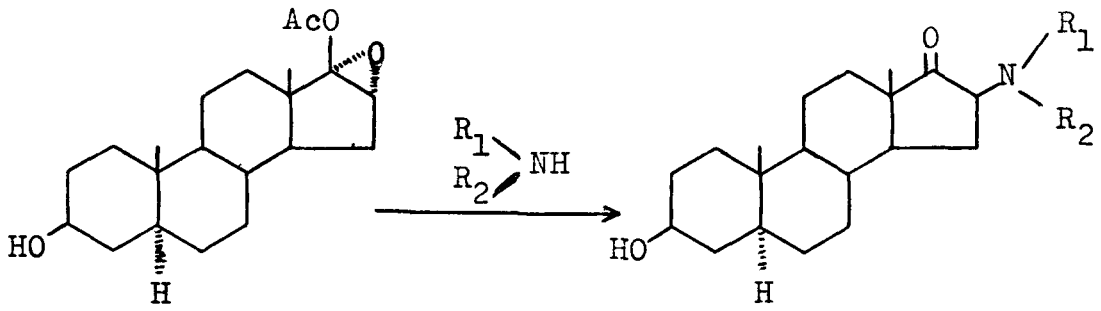
3,17-Dioxy-2-amino-steroid (LXI) was prepared by the condensation of 1α,2α-epoxy-5α-androstane-3,17-dione with boiling aqueous morpholine (LX)[16].



(LX) (LXI)

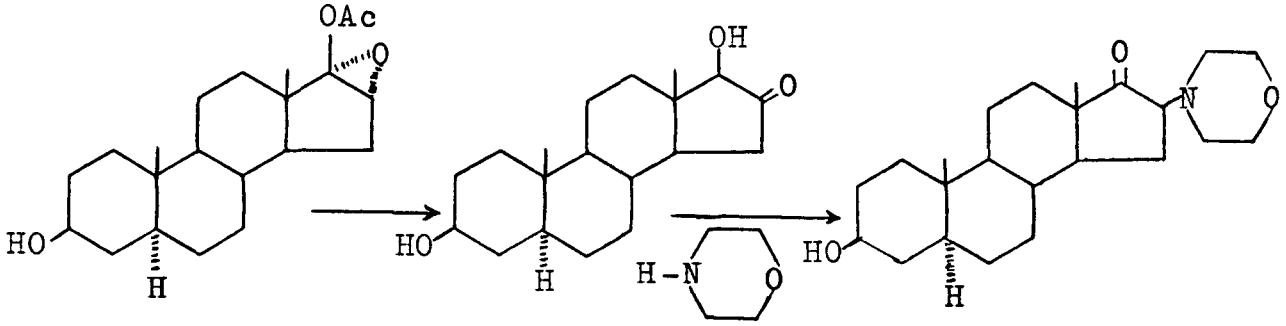
In the hope of potentiating the sedative activity[17] of 3α-hydroxy-2β-morpholino-5α-androstan-17-one, 11-oxo group was introduced in order to enhance the sedative potency and anaesthetic activity[18,19].

Savage et al.[20] utilized the condensation of 17β-acetoxy-16α,17α-epoxy-5α-androstane (LXII) with secondary amine to give tertiary 16β-amino-17-ketone (LXIII).



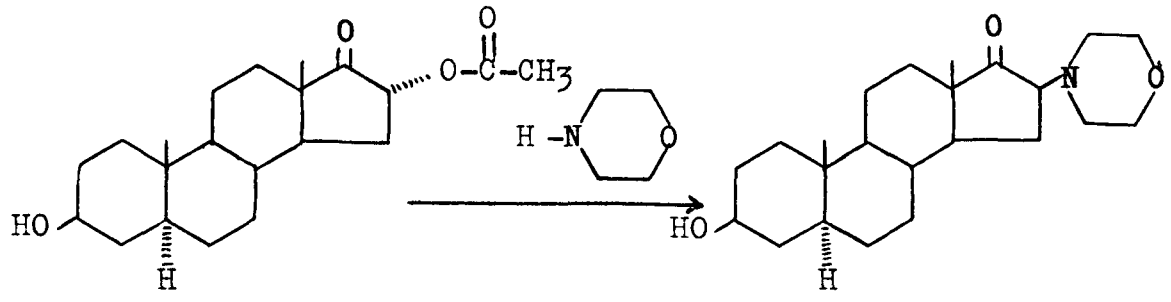
(LXII) (LXIII)

Hewett and Savage[21] carried out the rearrangement of 17β-acetoxy-16α,17α-epoxide (LXII) in aqueous alkali and obtained 17β-hydroxy-16-ketone (LXIV) which was condensed with morpholine to give 16β-morpholino-17-ketone (LXV).



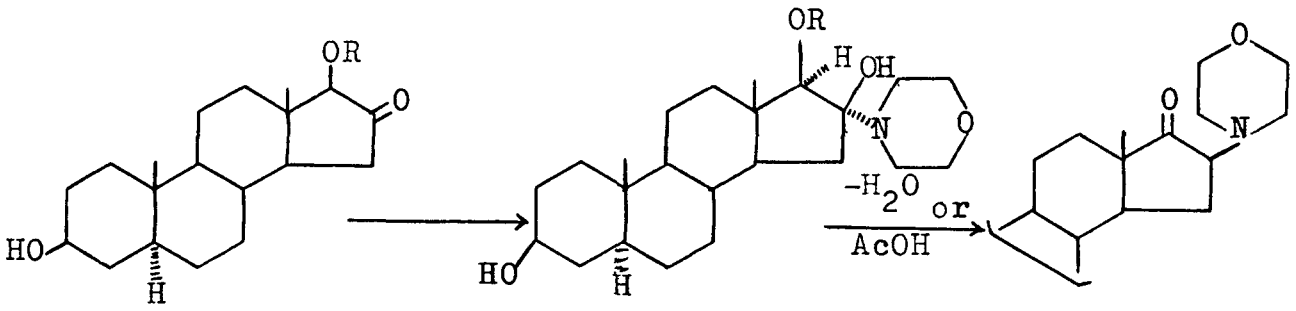
(LXII) (LXIV) (LXV)

Similarly the condensation of the 16α-acetate (LXVI) gave the 16β-morpholino-17-ketone (LXV)[21] on treatment with anhydrous morpholine.



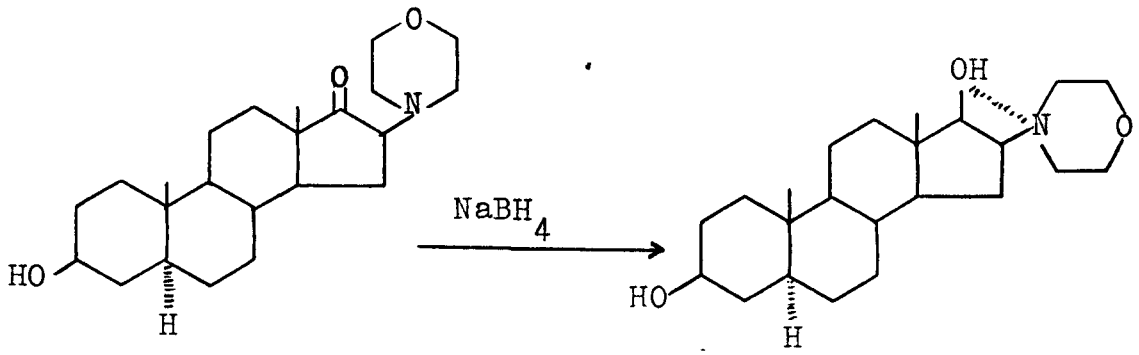
(LXVI) (LXV)

In contrast, the 17β-hydroxy-16-ketone (LXIV) and its 17-acetate (LXIVa) both gave 16β-morpholino-17-ketone (LXV) on condensation with morpholine, through α-attack on 16-carbonyl group to give the carbinols (LXVII) and (LXVIII) which undergo trans-elimination of water/acetic acid to give LXV[21].



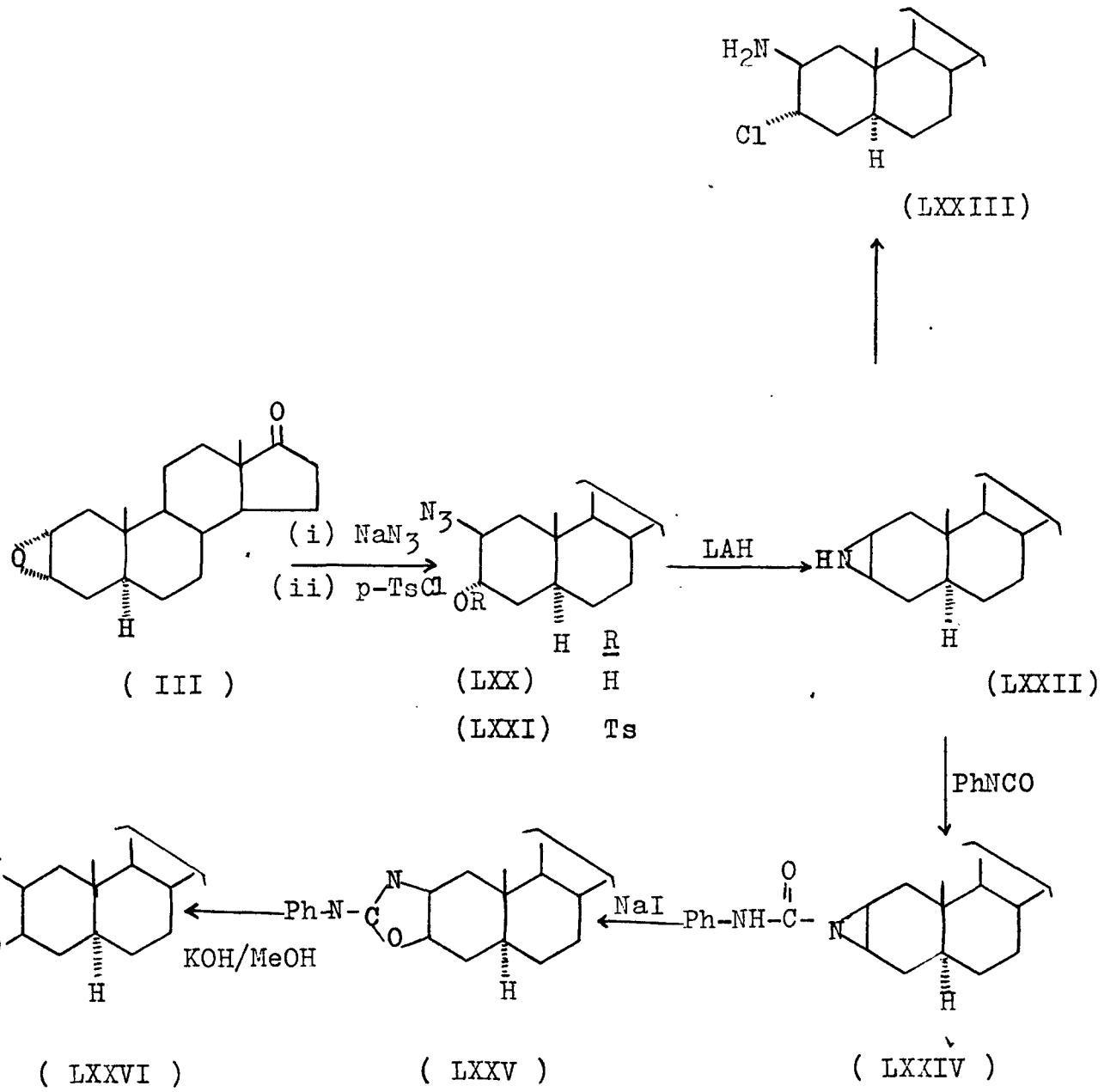
	R		R	
(LXIV)	H	(LXVII)	H	(LXV)
(LXIVa)	Ac	(LXVIII)	Ac	

Reduction of 16β-morpholino-17-ketone (LXV) with sodium borohydride gave cis 16β-morpholino-17β-ol (LXIX), which showed hydrogen bonding between the 17β-hydroxy group and 16β-nitrogen atom[21].

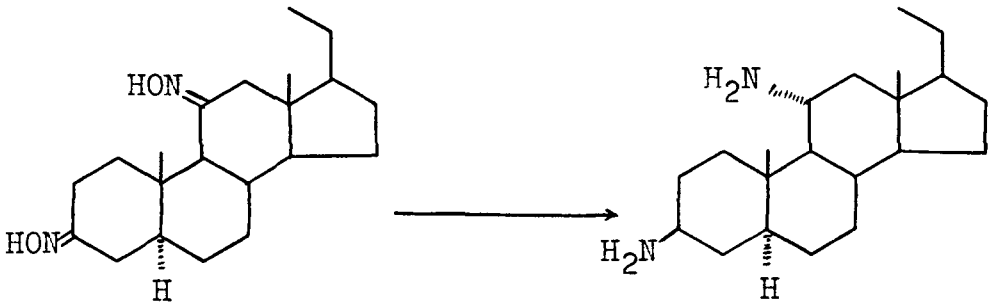


(LXV) (LXIX)

Ponsold and Preibsch[22] synthesized 2β,3β-imino-5α-androstan-17β-ol (LXXII) from 2α,3α-epoxy-5α-cholestan-17-one (III) via the corresponding azidoalcohol tosylate (LXXI) and converted into 2β-amino-3α-chloro-5α-androstan-17-ol (LXXIII). 2β-Amino-3β-hydroxy derivatives were prepared from aziridine (LXXII).

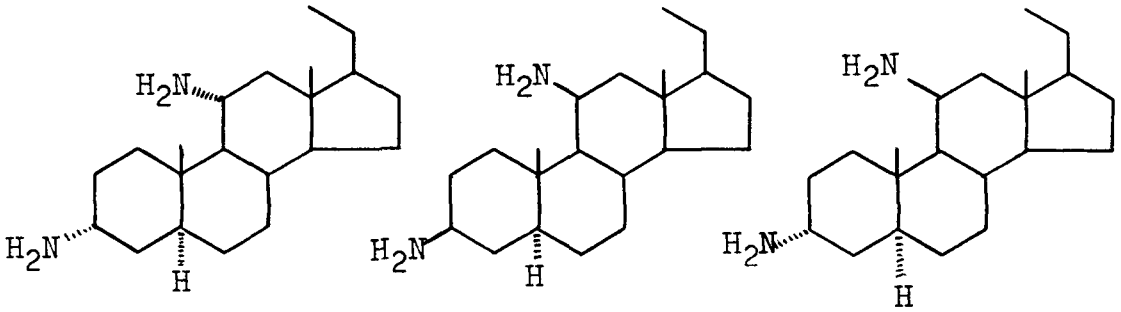


Campbell et al.[23] prepared 3β,11α-diamino-5α-pregnane (LXXVIII), by reduction of the dioxime (LXXVII) with sodium in propan-1-ol, in 30% yield as the dihydrochloride.



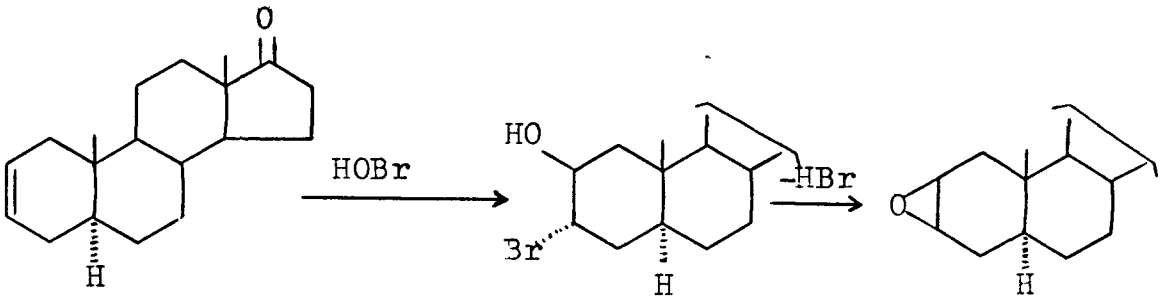
(LXXVII) (LXXVIII)

Similar set of reactions such as reduction with sodium in propan-1-ol, $LiAlH_4$ or catalytic hydrogenation were used for preparing other amino steroids LXXIX, LXXX and LXXXI[23]. Ponsold and Klemm[24] introduced equatorial amino groups (3β- and 11α-) by alkali metal reduction of the oxime, the axial 3α-amino group by reduction of 3α-azide; and the axial 11β-amino group by catalytic hydrogenation of the oxime.

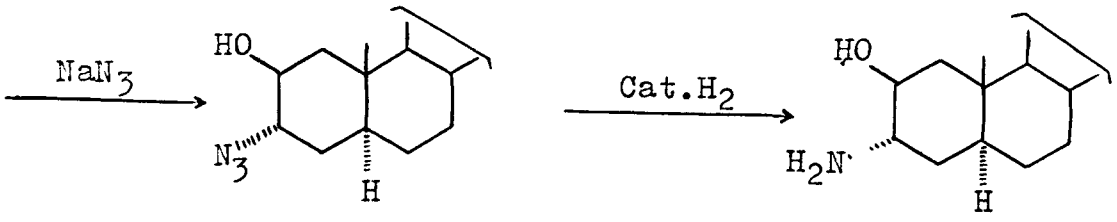


(LXXIX) (LXXX) (LXXXI)

Campbell et al.[25] synthesized and evaluated the 3-amino-2-hydroxy and 2-amino-3-hydroxy isomers. The Δ^2- 17-ketone (LXXXII) was converted to 2β,3β-epoxide (LXXXIV) via bromohydrin (LXXXIII). Trans diaxial ring opening[26] of epoxide (LXXXIV) by sodium azide gave the sole product 2β-hydroxy-3α-azide (LXXXV), which was converted to amine (LXXXVI) by catalytic hydrogenation.

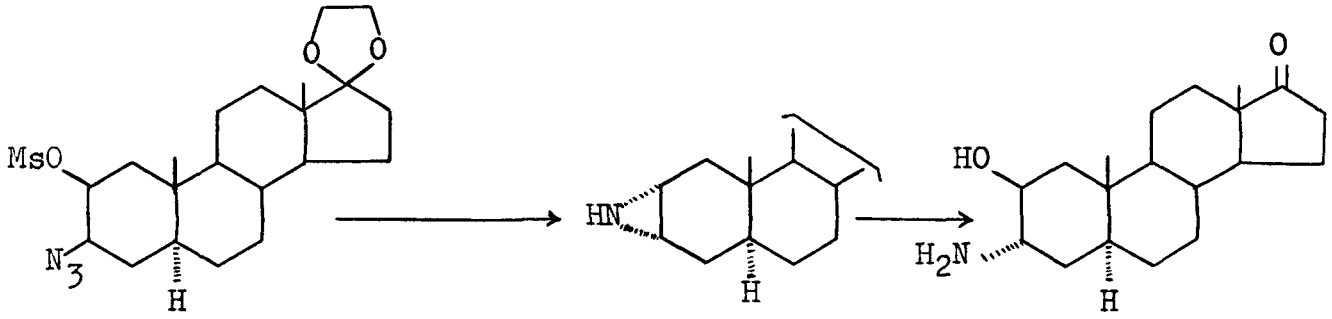


(LXXXII) (LXXXIII) (LXXXIV)



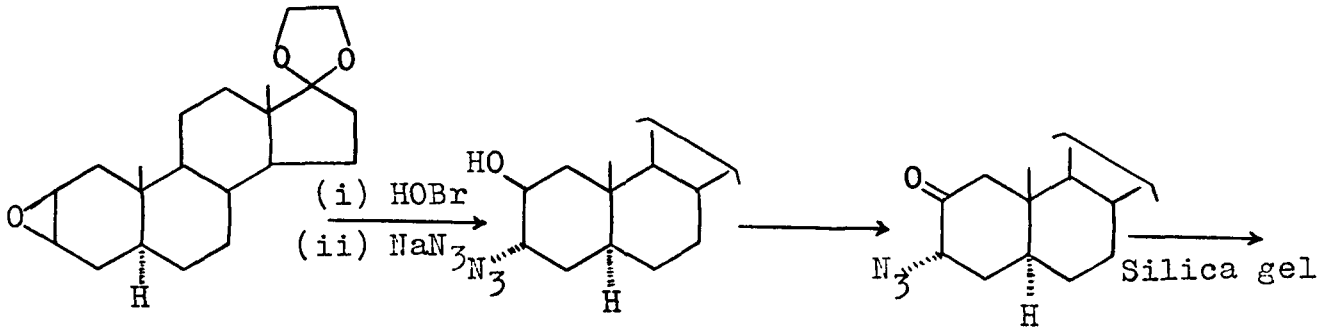
(LXXXV) (LXXXVI)

Mesylate (LXXXVIII) on $LiAlH_4$ reduction gave α-aziridine (LXXXVIII) which on hydrolysis with aqueous sulphuric acid afforded 2β-hydroxy-3α-amine (LXXXVI).

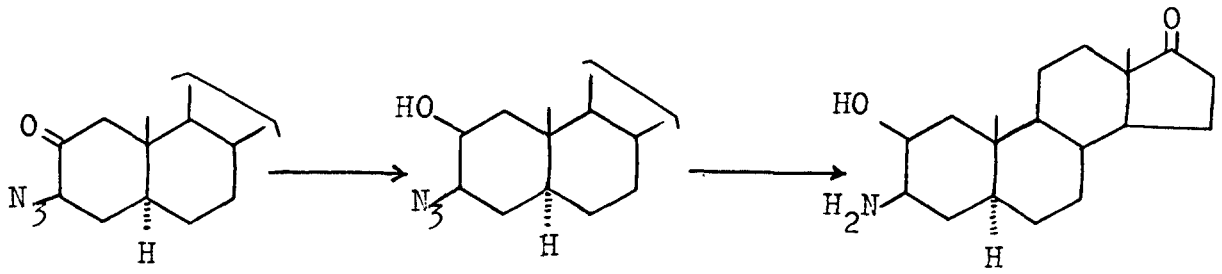


(LXXXVII) (LXXXVIII) (LXXXVI)

The 2β-hydroxy-3β-amino steroid (XCIV) was also obtained from the β-epoxide (LXXXIX) via the azide alcohol (XC), which was acetylated and then oxidized with buffered pyridinium chlorochromate, to give the 2-oxo-3α-azido-17-acetal (XCI). Reduction of (XCI) follwed by hydrolysis gave (XCIV).

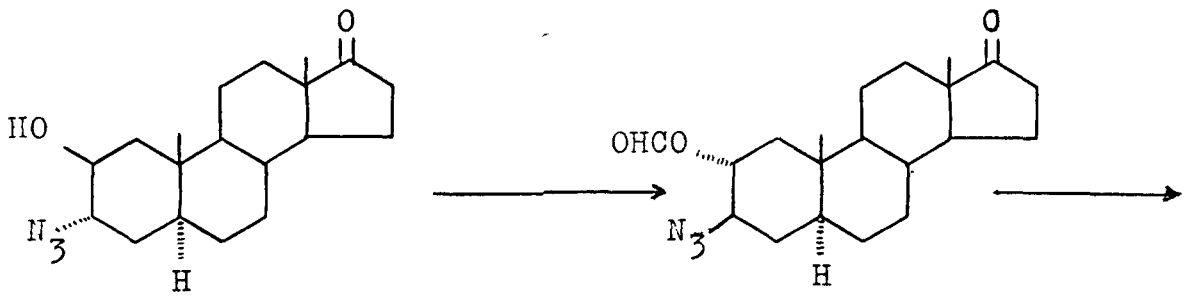


(LXXXIX) (XC) (XCI)

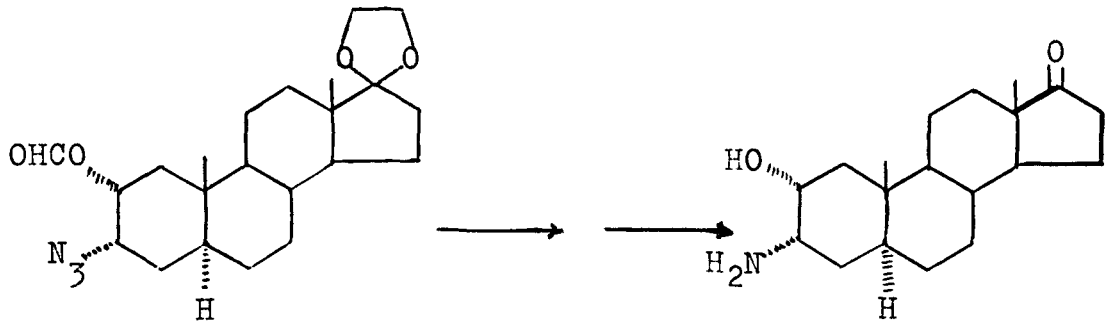


(XCII) (XCIII) (XCIV)

The 2α-hydroxy-3α-amine (XCVII) was prepared from azido alcohol (LXXXV)[25].

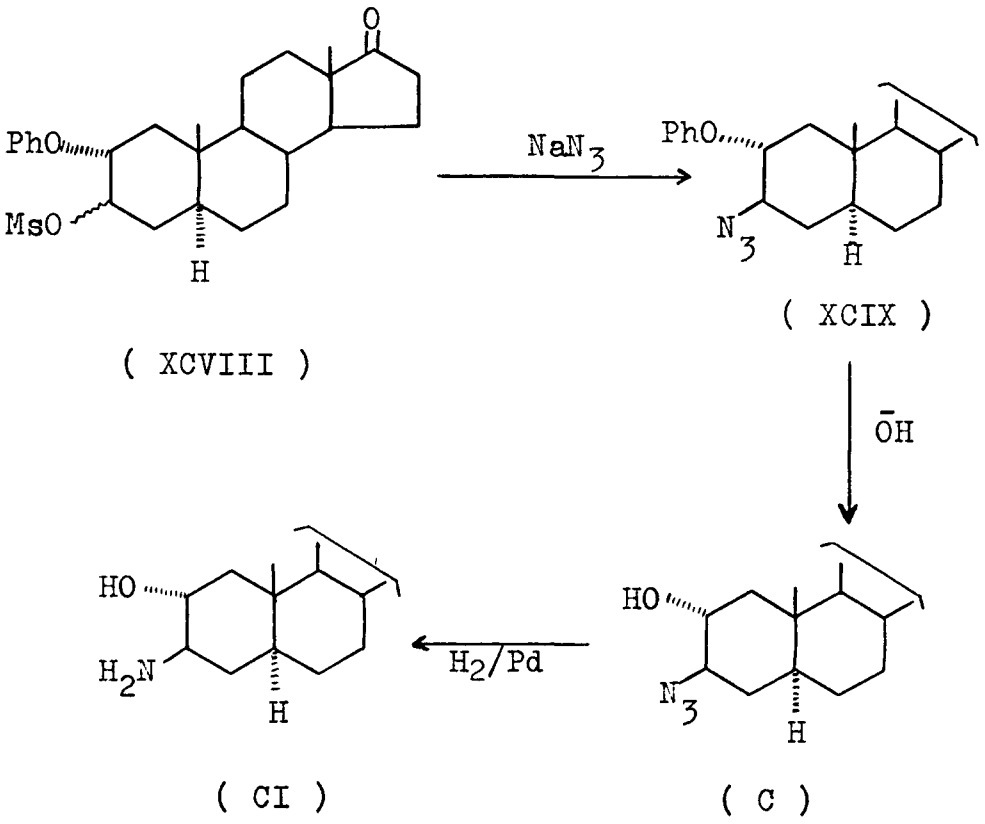


(LXXXV) (XCV)



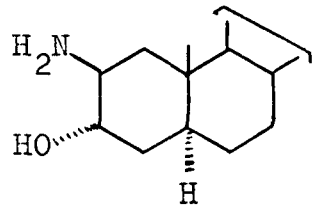
(XCVI) (XCVII)

The diequatorial 2α-hydroxy-3β-amine (CI) was prepared via mesylate (XCVIII), displacement of which with sodium azide gave 3β-azide (XCIX) which was hydrolyzed to the azido alcohol (C) and reduced (H_2/Pd) to the diequatorial amino alcohol (CI)[25].

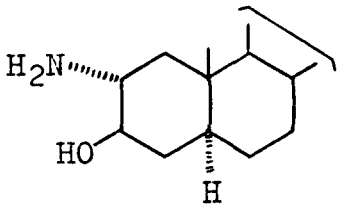


(XCVIII) (XCIX) (C) (CI)

The 2β-amino-3α-hydroxy steroid (CII) was obtained directly from the α-epoxide (III) by trans diaxial ring opening with ammonia[27]. Similar synthesis of 2α-amino-3β-hydroxy steroid (CIII) has also been reported.

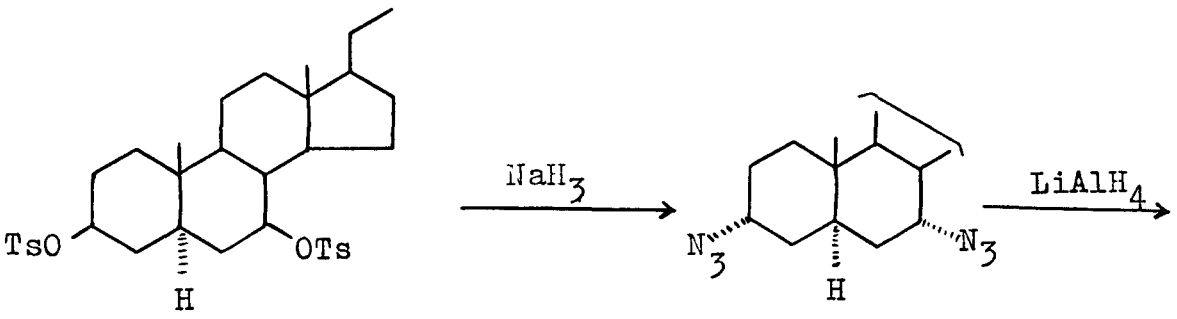


(CII)

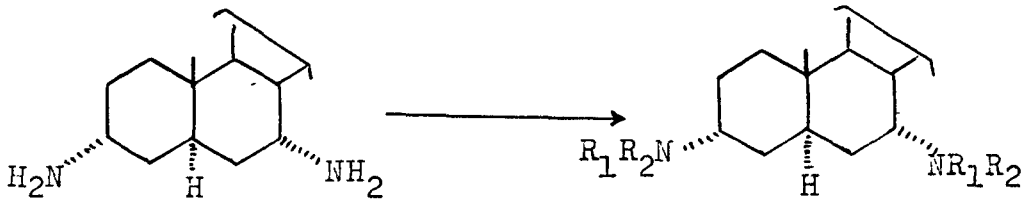


(CIII)

Campbell et al.[28] prepared 3,7-diamino-5α-pregnane (CVI) from 3β,7β-dihydroxy-5α-pregnane ditosylate (CIV) by reacting the latter with sodium azide which converted it to 3α,7α-diazido-5α-pregnane (CV). Reduction of CV by $LiAlH_4$ afforded 3α,7α-diamino-5α-prgnane (CVI). The diamine (CVI) was converted into the bisdimethylamino (CVII), diacetatamido (CVIII) and diformamido (CIX) derivatives by standard procedures[28].



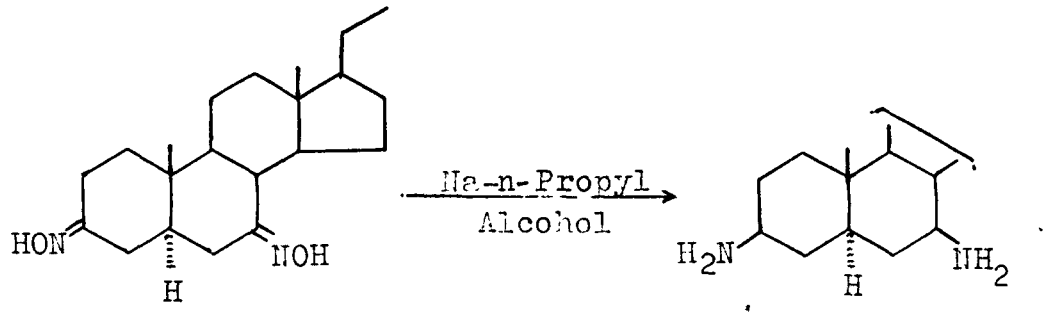
(CIV) (CV)



(CVI)

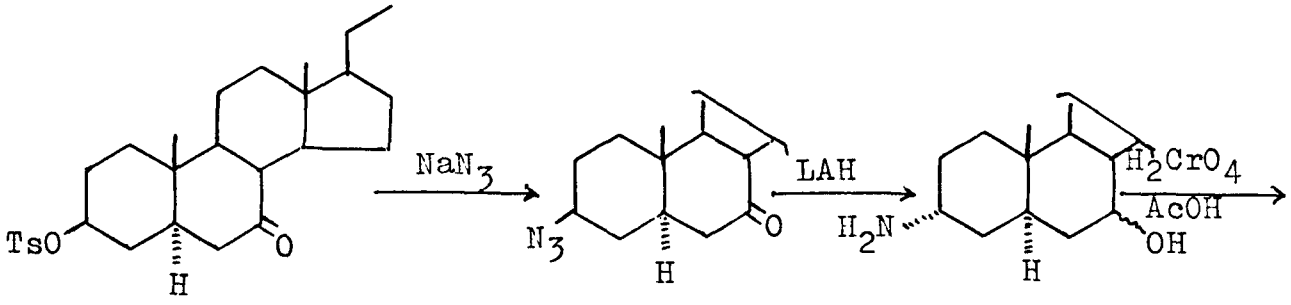
	R_1	R_2
(CVII)	CH_3	CH_3
(CVIII)	H	Ac
(CIX)	H	CHO

3β,7β-Diamino-5α-pregnane (CXI) was prepared by the reduction of the diketoxime (CX) with sodium-n-propyl alcohol[28].

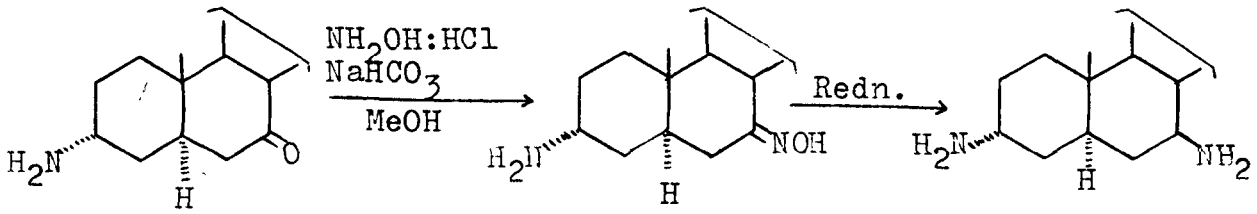


(CX) (CXI)

3α,7β-Diamino-5α-pregnane (CXIII) was prepared from CXII through the following sequence of reactions[28].

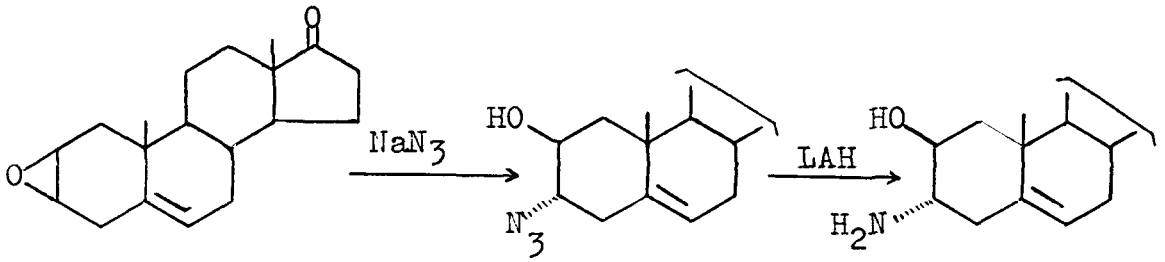


(CXII)

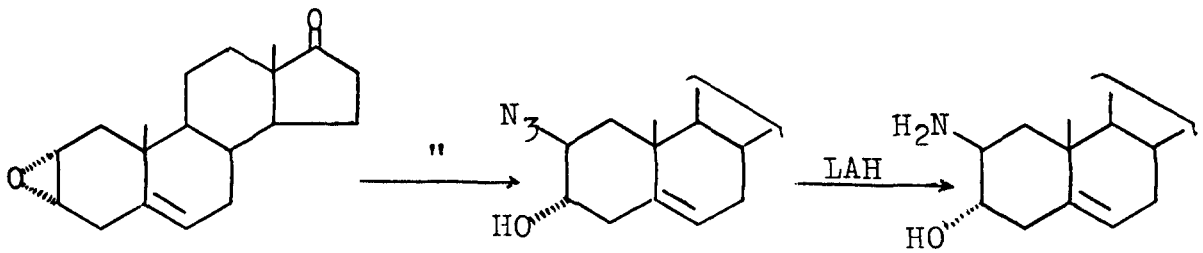


(CXIII)

Campbell et al.[29] carried out the stereospecific synthesis of 3α-amino-2β-hydroxyandrost-5-en-17-one (CXV) and 2β-amino-3α-hydroxyandrost-5-en-17-one (CXVII) from Δ^5-2β,3β-epoxyandrost-5-en-17-one (CXIV) and its 2α,3α-epimer (CXVI) respectively.

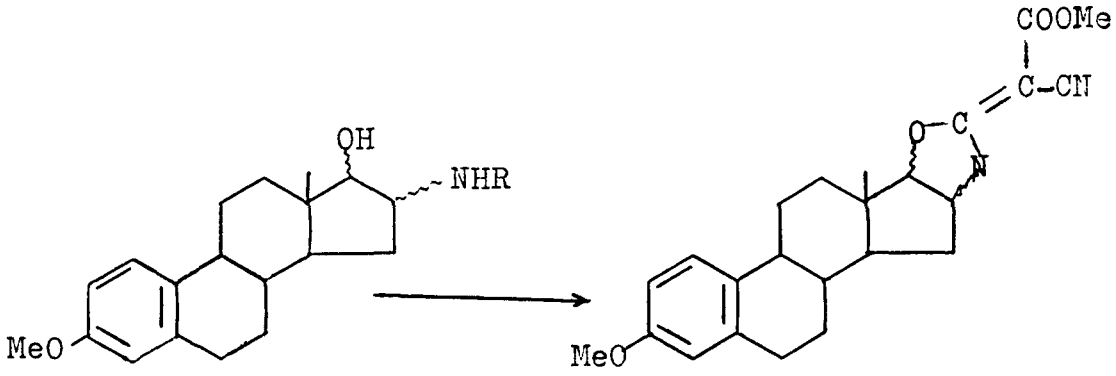


(CXIV) (CXV)



(CXVI) (CXVII)

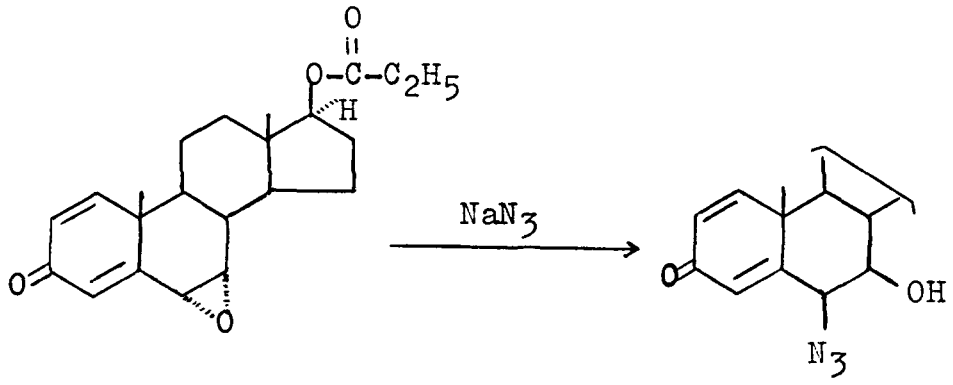
Molekularbiol and Shoenecker[30] reacted $(MeS)_2\ C{=}\underset{CN}{C}\text{-}COOMe$ with CXVIII, to produce derivative CXIX which gave a cyclic product (CXX). The reaction was stated to be used to study the configuration of vicinal amino alcohols.



	R
(CXVIII)	H
(CXIX)	$-C(SCH_3){=}C(CN)\text{-}COOCH_3$

(CXX)

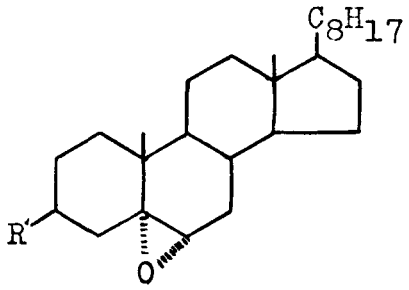
Kocor et al.[31] treated epoxyandrostadienone (CXXI) with NaN_3 in acetic acid at room temperature which gave azido-androstadiene (CXXII) in 40% yield.



(CXXI) (CXXII)

DISCUSSION

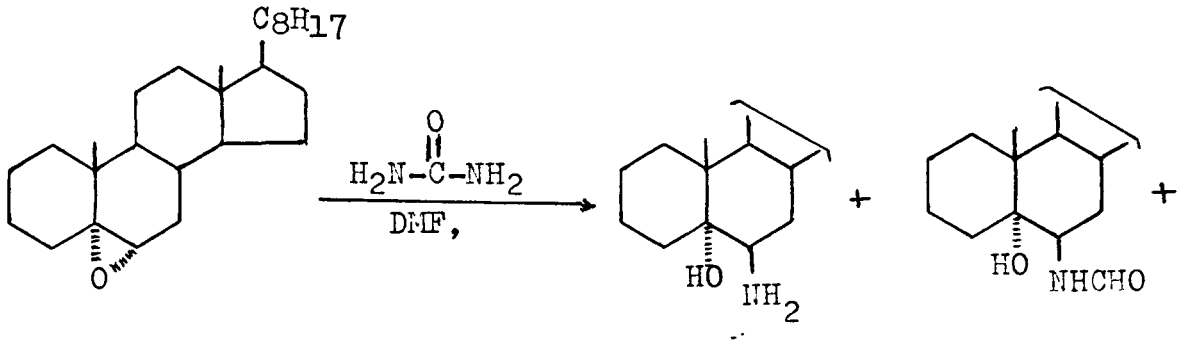
The synthesis of aminosterols, particularly the vicinal amino alcohols, has drawn the attention of chemists for the last so many years due to their non-hormonal biological activities[6,16]. A number of synthetic routes have been adopted by different workers. We have made an attempt to synthesize these compounds by treating some of the steroidal epoxides in the cholestane series with urea and obtained some interesting compounds. The epoxides selected for the present study are 5,6α-epoxy-5α-cholestane (CXXIII), 3β-chloro-5,6α-epoxy-5α-cholestane (CXXIV) and 3β-acetoxy-5,6α-epoxy-5α-cholestane (CXXV).



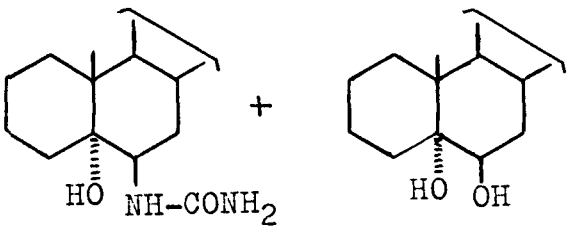
	R
(CXXIII)	H
(CXXIV)	Cl
(CXXV)	OAc

Reaction of 5,6α-epoxy-5α-cholestane (CXXIII) with urea

5,6α-Epoxy-5α-cholestane (CXXIII) was treated with urea in dimethylformamide and the reaction mixture was heated under reflux for 8 hrs. After the completion of reaction, the reaction mixture was worked up in usual manner, and chromatographed over silica gel to provide four compounds, m.p . 137°, 121°, 148° and 108°.



(CXXIII) (CXXVI) (CXXVII)



(CXXVIII) (CXXIX)

Characterization of the compound, m.p. 137°, as 5-hydroxy-6β-amino-5α-cholestane (CXXVI)

The mass spectrum of the compound, m.p. 137°, showed molecular ion peak at m/z 403 and was analysed correctly for $C_{27}H_{49}NO$. The IR spectrum of the compound showed strong absorption band around 3480 cm^{-1} which was assigned to -OH and -NH groups. The NMR spectrum of the compound exhibited a doublet at δ 4.4 (J = 8 Hz) integrating for two protons which could be assigned to $-N\underline{H}_2$. A multiplet was observed at δ 3.4 which was assigned to C6α-$\underline{H}$ ($W\frac{1}{2}$ = 6 Hz) and another broad singlet was seen at δ 4.1 was due to hydroxy proton which disappeared on D_2O exchange. The other signals were seen at δ 1.1 (C10β-$C\underline{H}_3$), 0.65 (C13β-$C\underline{H}_3$), and 0.85, 0.77 (other methyl protons). The above spectral and elemental analysis suggested the structure of the compound as 5-hydroxy-6β-amino-5α-cholestane (CXXVI).

Characterization of the compound, m.p. 121° as 5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXVII)

The compound m.p. 121°, was analysed correctly for $C_{28}H_{49}NO_2$ and showed a molecular ion peak in mass spectrum at m/z 431. The IR spectrum of the compound showed a strong absorption band around 1700 cm^{-1}. This indicated the presence of an amide group (amide I) in the molecule[32]. The strong band at 3500 cm^{-1} was due to -OH and -NH groups.

Another band at 1535 cm^{-1} showed the presence of formamido (-NH-CHO) group. The NMR spectrum displayed a sharp singlet at δ 8.03 which may be accounted for an aldehydic proton. A multiplet appeared at δ 4.73 was ascribed for -N<u>H</u>- proton. The C6α-<u>H</u> appeared at δ 3.5 as a multiplet and a multiplet at δ 2.35 which disappeared on D_2O exchange was due to -O<u>H</u>. Methyl signals were seen at δ 1.1 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$), 0.9 and 0.83 (other methyl protons). The foregoing discussion suggested the structure of the compound as 5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXVII).

<u>Characterization of the compound, m.p. 148° as 5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXVIII)</u>

The mass spectrum of compound (CXXVIII) m.p. 148°, showed a molecular ion peak at m/z 446 and analysed correctly for $C_{28}H_{50}N_2O_2$. The IR spectrum of the compound showed absorption peak at 3450 cm^{-1} for -OH and -NH- groups. Amide group[32] of urea linkage was shown by a band at 1690 (amide I) and 1510 cm^{-1} (amide II). The NMR spectrum of the compound showed a multiplet integrating for three protons attached to nitrogen atoms at δ 4.63. The C6α- proton was exhibited at δ 4.15 as a multiplet. Hydroxy proton appeared as a multiplet at δ 3.1 which disappeared on D_2O exchange. Other signels were present at δ 1.0 (C10β-C<u>H</u>$_3$), 0.73 (C13β-C<u>H</u>$_3$), 0.92 and 0.86 (other methyl protons). Thus on the basis of

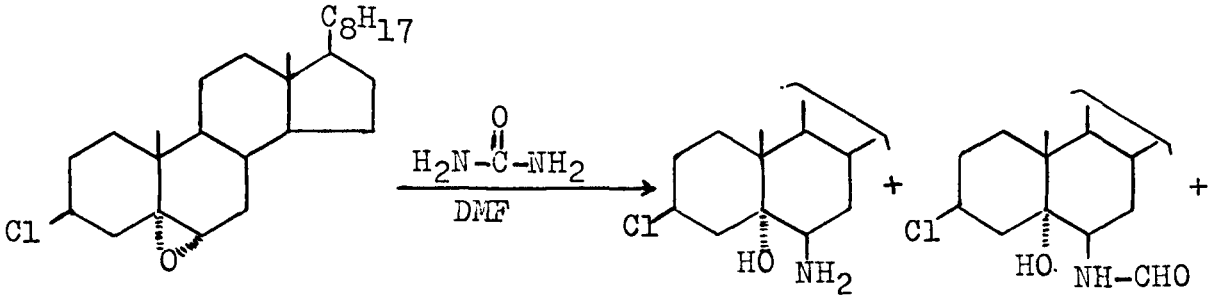
spectral and elemental analysis the structure of the above compound was established as 5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXVIII).

Characterization of the compound, m.p. 108°, as 5,6β-dihydroxy-5α-cholestane (CXXIX)

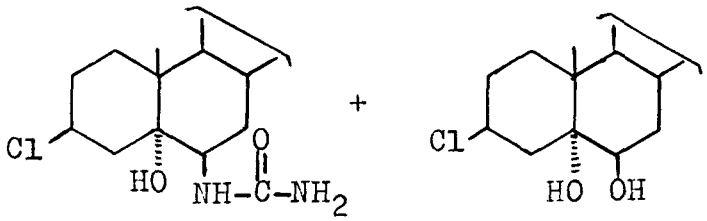
The compound, m.p. 108°, was analysed for $C_{27}H_{48}O_2$. The IR spectrum showed absorption band at 3400 cm^{-1} for -OH. The compound showed identical chemical, physical and spectral properties with an authentic sample of 5,6β-dihydroxy-5α-cholestane (CXXIX) (reported[33] m.p. 109°).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (CXXIV) with urea

The epoxide (CXXIV) was treated with urea in dimethylformamide under reflux conditions for 8 hrs. The reaction mixture, after usual work up and column chromatography over silica gel, afforded four compounds m.p . 173°, 151-153°, 175-177° and 123°.



(CXXIV) (CXXX) (CXXXI)



(CXXXII) (CXXXIII)

Characterization of compound, m.p. 173°, as 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (CXXX)

The compound, m.p. 173° showed molecular ion peaks at m/z 437/439 in mass spectrum. It was analysed for $C_{27}H_{48}NOCl$ and showed positive Beilstein test. The IR spectrum of the compound exhibited absorption peaks at 3590 and 3445 cm^{-1} for -OH and -NH groups. The NMR spectrum displayed a broad singlet at δ 8.2 for -O<u>H</u> proton which disappeared on D_2O addition. A multiplet at δ 3.5 was assigned to C6α-<u>H</u>, ($W\frac{1}{2}$ = 6 Hz) indicating that the amino group was axial[34]. The presence of a broad multiplet centred at δ 4.46 integrating for two protons was due to -N<u>H</u>$_2$. The C3α-<u>H</u> appeared at δ 4.3 as a multiplet ($W\frac{1}{2}$ = 17 Hz). Methyl signals were seen at δ 1.2 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$), 0.73 and 0.83 (other methyl protons). The foregoing discussion suggested the structure of the above compound as 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (CXXX).

Characterization of compound, m.p. 151-153°, as 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXI)

The mass spectrum of the compound, m.p. 151-153° showed molecular ion peaks at m/z 465/467 and was analysed for $C_{28}H_{48}NO_2Cl$. It gave positive Beilstein test. The IR spectrum of the compound showed strong absorption peak at 3470 cm^{-1} for -OH and -NH groups. The band at 1700 cm^{-1} (amide I) indicated the presence of a carbonyl group in the molecule. The formamido group gave its characteristic absorption bands at 1540 cm^{-1} (amide II)[32]. The NMR spectrum of the compound displayed a sharp singlet at δ 8.1 integrating for one proton of the formyl group. A multiplet for one proton was seen at δ 4.9 which could be assigned to -NH- proton. A broad singlet at δ 4.2 was due to -OH proton which disappeared on D_2O exchange. The multiplet for C3α-H and C6α-H appeared at δ 3.48. The methyl signals were present at δ 1.15 (C10β-CH_3), 0.7 (C13β-CH_3), 0.93 and 0.83 (other methyl protons). On the basis of above evidences the compound was identified as 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXI).

Characterization of compound, m.p. 175-177° as 3β-chloro-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXII)

The compound, m.p. 175-177°, showed molecular ion peaks at m/z 480/482 in it mass spectrum and was analysed for $C_{28}H_{49}N_2O_2Cl$. It showed positive Beilstein test. The IR

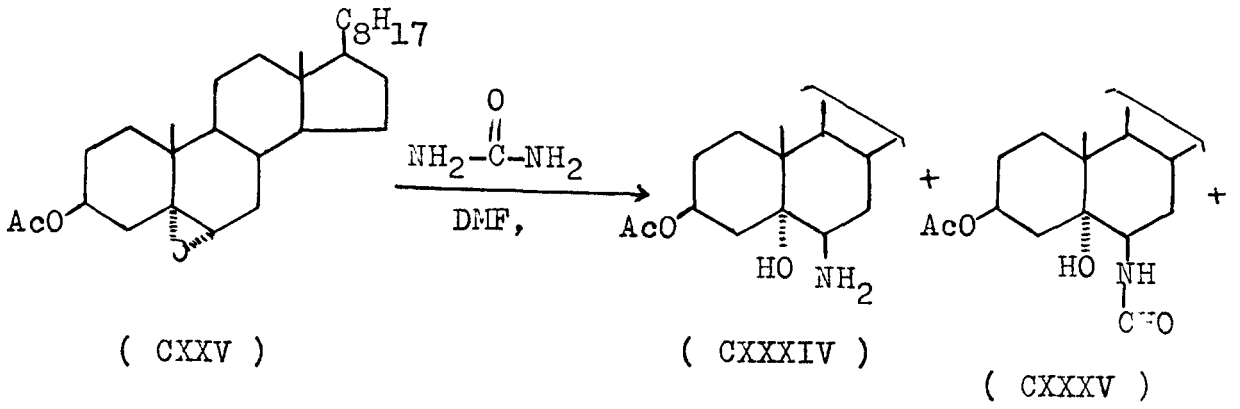
spectrum showed absorption bands at 3540 and 3400 cm^{-1} for -OH and -NH groups. Amide group of urea linkage was shown by bands at 1690 (amide I) and 1515 cm^{-1} (amide II)[32]. The NMR spectrum showed a multiplet at δ 6.5 integrating for one proton which could be assigned to -NH- proton (-NH-CO-NH_2). A doublet appearing at δ 4.15 (J = 8 Hz), integrating for two protons was assigned to -NH_2 protons. Another multiplet at δ 4.3 was due to C3α-H ($W\frac{1}{2}$ = 17 Hz). A multiplet appeared at δ 3.6 was ascribed for C6α-H. Hydroxy proton signal was seen at δ 6.4 as a broad singlet. Methyl signals were seen at δ 1.15 (C10β-CH_3), 0.7 (C13β-CH_3), 0.9 and 0.8 (other methyl protons). On the basis of above discussion the compound was identified as 3β-chloro-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXII).

Characterization of the compound, m.p. 123° as 3β-chloro-5,6α-dihydroxy-5α-cholestane (CXXXIII)

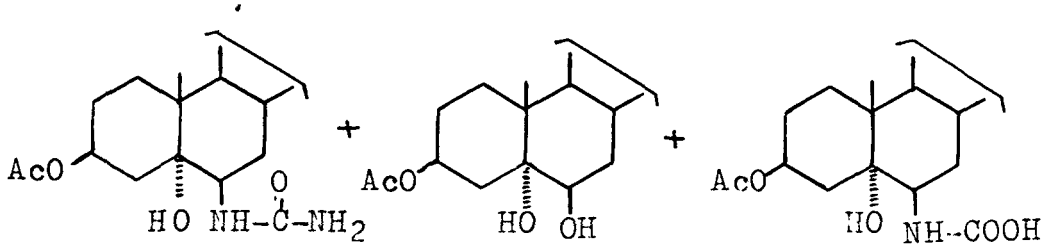
The compound, m.p. 123° was analysed correctly for $C_{27}H_{47}O_2Cl$. The IR spectrum exhibited strong absorption band at 3450 cm^{-1} for -OH group. No other significant bands were observed in IR spectrum of the compound m.p. 123°. The physical and spectral values were compared and found identical with authentic sample of 3β-chloro-5,6β-dihydroxy-5α-cholestane (CXXXIII)(reported[35] m.p. 125-126°).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CXXV) with urea

The epoxide (CXXV) was heated under reflux with urea in dimethylformamide for 8 hrs. The usual work up of the reaction mixture and column chromatography over silica gel provided five compounds m.p . 226-228°, 200-203°, 256-258°, 208° and an oil.



(CXXV) (CXXXIV) (CXXXV)



(CXXXVI) (CXXXVII) (CXXXVIII)

Characterization of compound, m.p. 226-228° as 3β-acetoxy-5-hydroxy-6β-amino-5α-cholestane (CXXXIV)

The mass spectrum of the compound, m.p. 226-228° showed a molecular ion peak at m/z 461 and was analysed correctly for $C_{29}H_{51}NO_3$. The IR spectrum of the compound exhibited a strong band at 3480 cm^{-1} for -NH- and -OH absorption. The other peaks were at 1730 (-O<u>C</u>OCH_3), 1290 and 1040 cm^{-1} (C-O). The NMR spectrum of the compound displayed a broad singlet at δ 9.2 for -O<u>H</u> which disappeared on D_2O shake. C3α-<u>H</u> was exhibited at δ 4.85 as multiplet ($W\frac{1}{2}$ = 18 Hz). Another multiplet at δ 4.5 integrating for two protons was ascribed for -N<u>H</u>$_2$. The C6α-<u>H</u> appeared as a multiplet at δ 3.6. Methyl signals were observed at δ 2.09 (-O-COC<u>H</u>$_3$), 1.0 (C10β-C<u>H</u>$_3$), 0.65 (C13β-C<u>H</u>$_3$), 0.77 and 0.85 (other methyl protons). Thus on the basis of foregoing discussion the compound was identified as 3β-acetoxy-5-hydroxy-6β-amino-5α-cholestante (CXXXIV).

Characterization of the compound, m.p. 200-203°, as 3β-acetoxy-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXV)

The compound, m.p. 200-203° analysed correctly for $C_{30}H_{51}NO_4$ and showed molecular ion peak at m/z 489 in mass spectrum. The IR spectrum showed absorption bands at 3500 (-NH, -OH), 1740 (-O<u>C</u>O-CH_3) and 1700 cm^{-1} (-CHO). Formamido group showed its absorption bands at 1680 and 1540 cm^{-1} for amide I and amide II, respectively. The NMR spectrum of the

compound exhibited a sharp singlet at δ 8.1 for the formyl proton and a multiplet at δ 5.2 for C3α-H ($W\frac{1}{2}$ = 18 Hz). Another multiplet at δ 4.9 was assigned to -NH proton. The C6α-H was exhibited as a multiplet at δ 3.9 ($W\frac{1}{2}$ = 6Hz), suggesting that amino group is axial[34]. A singlet at δ 2.0 was ascribed for acetate methyl protons. Methyl signals were present at δ 1.13 (C10β-CH_3), 0.7 (C13β-CH_3), 0.9 and 0.8 (other methyl protons).

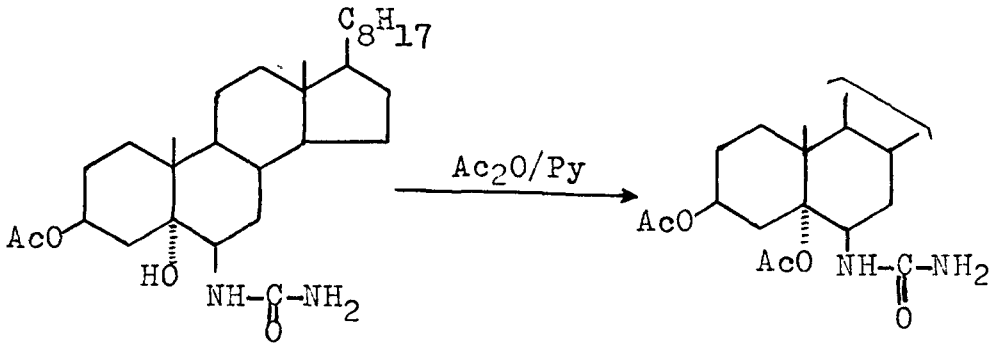
Characterization of the compound m.p. 256-258° as 3β-acetoxy-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXVI)

The mass spectrum of the compound, m.p. 256-258° showed molecular ion peak at m/z 504 and was analysed for $C_{30}H_{52}N_2C_4$. The IR spectrum of the compound showed strong absorption peak at 3450 cm^{-1} for -OH and -NH. The amide (-NH-CO-NH_2) function of the compound was indicated by a strong band at 1690(amide I) and 1515 (amide II) cm^{-1}[32]. The acetate carbonyl group was indicated by a band at 1730 cm^{-1}. The NMR spectrum of the compound displayed a multiplet at δ 5.2 for C3α-H ($W\frac{1}{2}$ =18 Hz) and a doublet (J = 8 Hz) at δ 4.73 for -NH- proton. A multiplet at δ 4.0 was due to C6α-H and $-NH_2$ protons. The methyl signal of acetate group appeared as a singlet at δ 2.0. The methyl signals were present at δ 1.1 (C10β-CH_3), 0.65 (C13β-CH_3), 0.85 and 0.77 (other methyl protons). On the

basis of forgoing discussion the above compound was identified as 3β-acetoxy-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXVI).

Acetylation of compound (CXXXVI)

The compound (CXXXVI) on acetylation with acetic anhydride and pyridine provided the acetylated product (CXXXIX), m.p. 201-204°.



(CXXXVI) (CXXXIX)

Characterization of compound m.p. 201-204° as 3β,5-diacetyoxy-6β-amino-N-amido-5α-cholestane (CXXXIX)

The mass spectrum of the compound, m.p. 201-204°, showed a molecular ion peak at m/z 546 and was analysed correctly for $C_{32}H_{54}N_2O_5$. The IR spectrum of the compound showed absorption peak at 3510 cm^{-1} for -NH- and -OH groups. The bands at 1680 and 1520 cm^{-1} were due to amide linkage. Other absorption band was at 1730 cm^{-1} ($CH_3-\underset{\underset{O}{\|}}{C}-O-$). The NMR spectrum of the

compound displayed a broad multiplet centred at δ 5.15 for C3α-H ($W\frac{1}{2}$ = 18 Hz) and a doublet (J = 8 Hz) for $-NH_2$ protons at δ 4.55. The C6α-H and -NH- protons were located at δ 4.1 as a broad multiplet. Two acetate methyl signals were indicated by two singlets at δ 2.1 and 2.0 each integrating for three protons. Methyl signals were seen at δ 1.1 (C10β-CH_3), 0.63 (C13β-CH_3), 0.86 and 0.76 (other methyl protons).

Characterization of the compound, m.p. 208° as 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (CXXXVII)

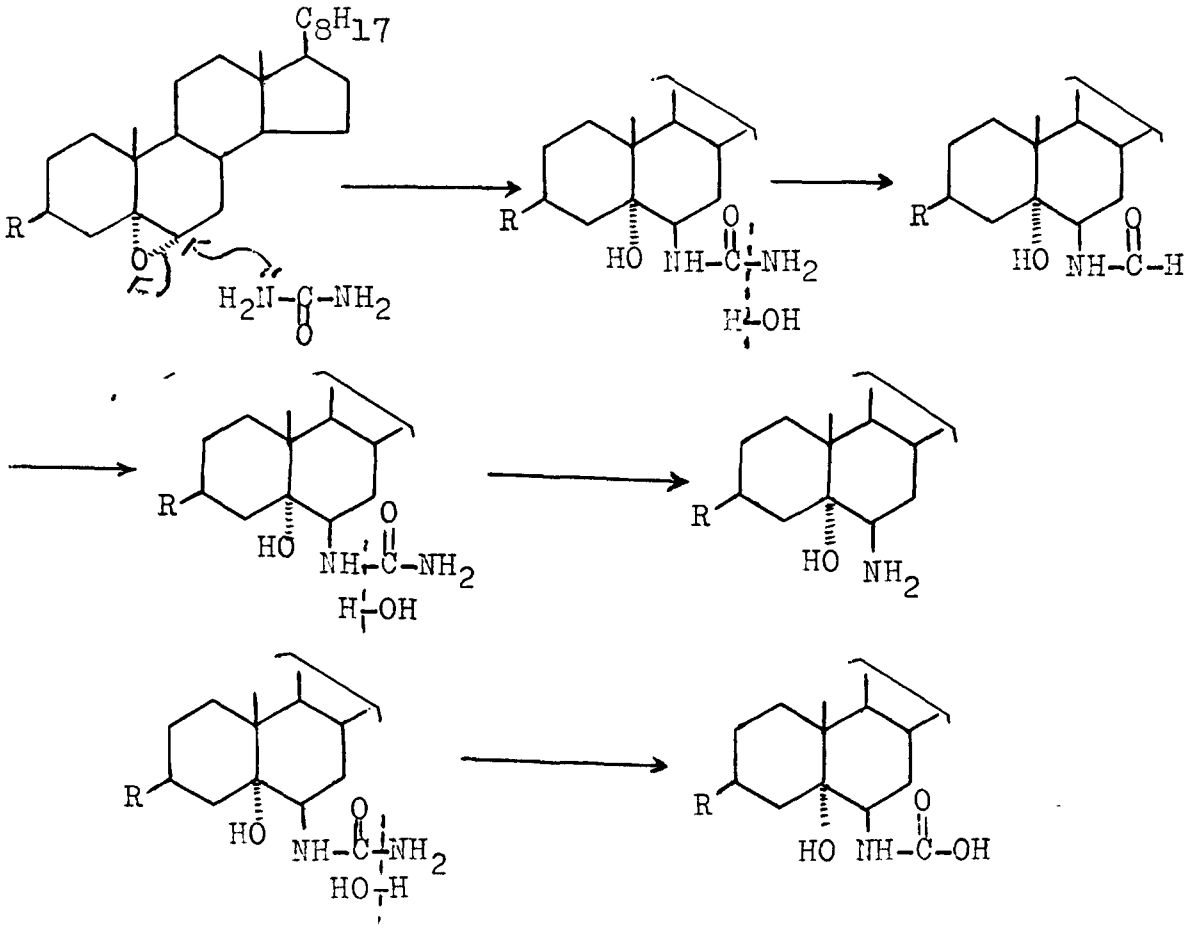
The compound, m.p. 208° was identified on the basis of its spectral and elemental analysis and comparison with authentic sample of the diol (CXXXVII) (m.p., m.m.p. and TLC) (reported[34] m.p. 209°).

Characterization of the compound, a non crystallizable oil as 3β-acetoxy-5-hydroxy-6β-amino-N-carboxy-5α-cholestane (CXXXVIII)

The mass spectrum of the compound showed molecular ion peak at m/z 461 and was analysed for $C_{29}H_{51}NO_5$. The IR spectrum of the compound showed absorption bands at 3480 (-NH, -OH), 1730 (-O-C(=O)-CH_3) and 1720 cm^{-1} (COOH). Amide group absorbed at 1680 (amide I) and 1540 cm^{-1} (amide II)[32]. The NMR spectrum of the compound showed broad singlets at δ 9.35 and 3.0 for -OH protons. Both the protons were exchangeable with D_2O.

The multiplets at δ 4.85, integrating for one proton, was ascribed for C3α-H and at δ 4.2 ($W\frac{1}{2}$ = 8 Hz) for C6α-H. Another multiplet at δ 5.2 was assigned to -NH-. The acetate methyl signal was exhibited at δ 2.0 as a singlet. Methyl signals were present at δ 1.0 (C10β-CH_3), 0.65 (C13β-CH_3), 0.85 and 0.77 (other methyl protons). The above spectral properties and elemental analysis suggested the structure of the above compound as 3β-acetoxy-5-hydroxy-6β-amino-N-carboxy-5α-cholestane (CXXXVIII).

The probable route for the formation of above discussed steroidal aminoalcohols has been shown in the following scheme.



It was suggested that the compound which was initially formed due to attack of urea on epoxide ring from the back side followed by trans diaxial[36] ring opening was responsible for the formation of the rest of the products. Hydrolysis of the amide group from different bonds has resulted various products described above.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were determined in nujol with a Perkin-Elmer 237 spectrophotometer. NMR spectra were run in $CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. The mass spectra were measured on a AIE MS-9 mass spectrometer. TLC plates were coated with silica gel (60-120 mesh). A 20% aqueous solution of perchloric acid was used as a spraying agent. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate was used as the drying agent. NMR values are given in p.p.m. (s=singlet, d = doublet, dd = double doublet, br = broad, m = multiplet centred at).

5,6α-Epoxy-5α-cholestane (CXXIII)

Cholest-5-ene (6 g) was dissolved in chloroform (40 ml) and treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform at -8° for 20 hrs. The mixture was then washed with ice cooled water, sodium bicarbonate solution (5%), water, sodium thiosulphate solution (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished CXXIII as an oil which was crystallized from acetone as needles (4.3 g), m.p. 76° (reported[34] m.p. 76°).

3β-Chloro-5,6α-epoxy-5α-cholestane (CXXIV)

Cholesteryl chloride (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice cooled sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water. Evaporation of the solvent yielded CXXIV as an oil which was crystallized from acetone as needles (8.1 g), m.p. 89° reported[35] m.p. 89.5-90.5°).

3β-Acetoxy-5,6α-epoxy-5α-cholestane (CXXV)

Cholesteryl acetate (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform and left at -8° for 20 hrs. The reaction mixture was then washed with ice cooled water, sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water. Evaporation of the solvent provided (CXXV) as semi-solid which was crystallized from acetone as needles (8.4 g), m.p. 97° (reported[34], m.p. 97°).

Reaction of 5,6α-epoxy-5α-cholestane (CXXIII) with urea: 5-Hydroxy-6β-amino-5α-cholestane (CXXVI), 5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXVII), 5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXVIII) and 5,6β-dihydroxy-5α-cholestane (CXXIX)

The mixture of 5,6α-epoxy-5α-cholestane (CXXIII) (2.5 g) and urea (2 g) (1:5 mole) was dissolved in dimethylformamide (100 ml) and it was heated under reflux for 8 hrs. The reaction was monitored with TLC till all the starting material was consumed. After the completion of the reaction, the reaction mixture was poured in water and extracted with ether. The ethereal layer was washed with water several times to remove unreacted urea and dried over anhydrous sodium sulphate. The solvent was evaporated on a water bath to yield a residue in the form of an oily mass which was chromatographed over silica gel (75 g). Elution with light petroleum-ethyl acetate (75:1) yielded 5-hydroxy-6β-amino-5α-cholestane (CXXVI) (380 mg) which was recrystallized from light petroleum, m.p. 137°.

Analysis Found : C, 80.37; H, 12.16; N, 3.45

$C_{27}H_{49}NO$ requires : C, 80.39; H, 12.15; N, 3.47%.

IR : $\nu_{max.}$ 3480 (-NH, -OH), 1280 and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 4.4 (d, J = 8 Hz, $N\underline{H}_2$), 4.1 (br s, -O$\underline{H}$, exchangeable with D_2O), 3.4 (m, C6α-$\underline{H}$), 1.1 (C10β-$C\underline{H}_3$), 0.65(C13β-$C\underline{H}_3$), 0.85 and 0.77 (other methyl protons).

MS : m/z 403 (M^+)

Further elution with light petroleum-ethyl acetate (10:1) furnished 5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXVII) (220 mg) as shining crystals, m.p. 121°.

Analysis Found : C, 78.00; H, 11.34; N, 3.20

$C_{28}H_{49}NO_2$ requires : C, 77.95; H, 11.36; N, 3.28%.

IR : $\nu_{max.}$ 3500 (-NH, -OH), 1700 and 1535 (-NHCHO), 1230 and 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 8.03 (s, -C<u>H</u>O), 4.73 (m, -N<u>H</u>-CHO), 3.5 (m, C6α-<u>H</u>), 2.85 (m,-O<u>H</u>), 1.1 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$), 0.91, and 0.83 (other methyl protons).

MS : m/z 431 (M^+), 413 ($M^+ - H_2O$).

Further elution with light petroleum-ethyl acetate (5:1) afforded 5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXVIII) (370 mg) which was recrystallized from light petroleum (315 mg), m.p. 148°.

Analysis Found : C, 75.34; H, 11.20; N, 6.30

$C_{28}H_{50}N_2O_2$ requires : C, 75.33; H, 11.21; N, 6.27%.

IR : $\nu_{max.}$ 3450 (-NH, -OH), 1690 and 1510 (-NH-C(=O)-NH$_2$), 1235 and 1045 cm^{-1} (C-O).

^{1}H-NMR : δ 4.63 (m,-N<u>H</u>-C(=O)-N<u>H</u>$_2$), 4.15 (m, C6α-<u>H</u>), 3.1 (m,-O<u>H</u>, exchangeable with D_2O), 1.0 (C10β-C<u>H</u>$_3$), 0.73 (C13β-C<u>H</u>$_3$), 0.92 and 0.86 (other methyl protons).

MS : m/z 446 (M^+).

Further elution with light petroleum-ethyl acetate (1:1) provided the known compound 5,6β-dihydroxy-5α-cholestane(CXXIX), recrystallized from light petroleum (170 mg), m.p. 108° (reported[34] m.p. 109°).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (CXXIV) with urea: 3β-Chloro-5-hydroxy-6β-amino-5α-cholestane (CXXX), 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXI), 3β-chloro-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXII) and 3β-chloro-5,6β-dihydroxy-5α-cholestane (CXXXIII)

The mixture of 3β-chloro-5,6α-epoxy-5α-cholestane (CXXIV) (2.5 g) and urea (2 g) (1:5 mole) was dissolved in dimethyl-formamide (100 ml) and was heated under reflux for 8 hrs. The reaction was monitored by TLC and after completion of the reaction, the reaction mixture was poured in water, worked up in usual manner and dried over anhydrous sodium sulphate. The solvent evpaoration over water bath yielded a residue which was column chromatographed over silica gel (75 g). Elution with light petroleum-ethyl acetate (20:1) and recrystallization from light petroleum afforded 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (CXXX) (345 mg) as needles, m.p. 173°.

Analysis Found : C, 73.94; H, 10.94; N, 3.17

$C_{27}H_{48}NOCl$ requires : C, 74.05; H, 10.97; N, 3.20%.

IR : $\nu_{max.}$ 3590 and 3445 (-NH, -OH), 1230 and 1050 (C-O), 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 8.2 (s, -O<u>H</u>, exchangeable with D_2O), 3.5 (m, C6α-<u>H</u>), 4.46 (m, -N<u>H</u>$_2$), 4.3 (m, $W_{\frac{1}{2}}$ = 17 Hz, C3α-<u>H</u>), 1.2 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$), 0.73 and 0.83 (other methyl protons).

MS : m/z 437/439 (M^+), 419/421 ($M^+ - H_2O$).

Further elution with light petroleum-ethyl acetate (15:1) provided 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXI), which was recrystallized from light petroleum (240 mg), m.p. 151-153°.

Analysis Found : C, 71.70; H, 10.27, N, 3.01

$C_{28}H_{48}NO_2Cl$ requires : C, 71.75; H, 10.31, N, 3.00%.

IR : $\nu_{max.}$ 3470 (-NH, -OH), 1700 (-CHO), 1540 (-NH-CHO), 1230, 1210, 1035 (C-O), 730 cm^{-1} (C-Cl).

^{1}H-NMR : δ 8.1 (s, -C<u>H</u>O), 4.9 (m, -N<u>H</u>-CHO), 4.2 (br s, -O<u>H</u>, exchangeable with D_2O), 3.48 (m, C3α-<u>H</u>, C6α-<u>H</u>), 1.15 (C10β-C<u>H</u>$_3$), 0.7 (C13β-C<u>H</u>$_3$), 0.93 and 0.83 (other methyl protons).

MS : m/z 465/467 (M^+), 447/449 ($M^+ - H_2O$).

Further elution with light petroleum-ehtyl acetate (1:1) gave 3β-chloro-5-hydroxy-6β-amino-N-amido-5α-cholestane(CXXXII) which was recrystallized from light petroleum (270 mg),

m.p. 175-177°.

Analysis Found : C, 69.89; H, 10.20; N, 5.73

$C_{28}H_{49}N_2O_2Cl$ requires : C, 69.92; H, 10.19; N, 5.82%.

IR : ν_{max}: 3540, 3400 (-NH, -OH), 1690 and 1515 ($-NH-CO-NH_2$), 1020 (C-O), 725 cm^{-1} (C-Cl).

^{1}H-NMR : δ 6.5 (m, -NH-CO-), 6.4 (br s, -OH, exchangeable with D_2O), 4.15 (d, J = 8 Hz, $-NH_2$), 4.3 (m, $W\frac{1}{2}$ = 17 Hz, C3α-H), 3.6 (m, C6α-H), 1.15 (C10β-CH_3), 0.7(C13β-CH_3), 0.9 and 0.8 (other methyl protons).

MS : m/z 480/482 (M^+), 462/464 ($M^+ - H_2O$).

Continued elution with the same solvent system afforded 3β-chloro-5,6β-dihydroxy-5α-cholestane (CXXXIII), recrystallized from light petroleum as needles (180 mg), m.p. 123°(reported[35] m.p. 125-126°).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CXXV) with urea: 3β-Acetoxy-5-hydroxy-6β-amino-5α-cholestane (CXXXIV), 3β-acetoxy-6β-amino-N-formyl-5α-cholestane (CXXXV), 3β-acetoxy-6β-amino-N-amido-5α-cholestane (CXXXVI), 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (CXXXVII), 3β-acetoxy-5-hydroxy-6β-amino-N-carboxy-5α-cholestane (CXXXVIII)

The mixture of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CXXV) (2.5 g) and urea (2 g) (1:5 mole) was dissolved in

dimethylformamide (100 ml) and was refluxed for 8 hrs. The progress of the reaction was monitored with TLC, when all of the starting material was consumed, the reaction mixture was worked up in ether and dried over anhydrous sodium sulphate. On the solvent evaporation, the residue left was column chromatographed over silica gel (75 g). Elution with light petroleum-ethyl acetate (9:1) and recrystallization from light petroleum gave 3β-acetoxy-5-hydroxy-6β-amino-5α-cholestane (CXXXIV) (120 mg), m.p. 226-228°.

Analysis Found : C, 75.41; H, 11.05; N, 3.05

$C_{29}H_{51}NO_3$ requires : C, 75.48; H, 11.06; N, 3.03%.

IR : $\nu_{max.}$ 3450 (-NH, -OH), 1730 (-O-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1690 and 1515 (-NH-CO-NH_2), 1290 and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 9.2 (br s, -O$\underline{H}$, disappears on D_2O exchange), 5.2 (m, $W\frac{1}{2}$ = 18 Hz, C3α-$\underline{H}$), 4.73 (m, -N$\underline{H}$-), 4.0 (m, C6α-$\underline{H}$, -N$\underline{H}_2$), 2.0 (s, -O-$\underset{\underset{O}{\|}}{C}$-C$\underline{H}_3$), 1.1 (C10β-C$\underline{H}_3$), 0.65 (C13β-C$\underline{H}_3$), 0.77 and 0.85 (other methyl protons).

MS : m/z 461 (M^+), 443 (M^+ - H_2O).

Further elution with light petroleum-ethyl acetate (4:1) and recrystallization from light petroleum provided 3β-acetoxy-5-hydroxy-6β-amino-N-formyl-5α-cholestane (CXXXV) (195 mg), m.p. 200-203°.

Analysis Found : C, 73.63, H, 10.40, N, 2.81

$C_{30}H_{51}NO_4$ requires : C, 73.61, H, 10.42, N, 2.86%.

IR : $\nu_{max.}$ 3500 (-NH and -OH), 1740 (-O-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1680, 1540 (-NH-CHO), 1280 (acetate) and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 8.1 (s, -CHO), 5.2 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H), 4.9(m, -NH-), 3.9 (m, C6α-H), 2.75 (br s, -OH, exchangeable with D_2O), 2.0 (s, -O-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1.13 (C10β-$CH_3$), 0.7(C13β-$CH_3$), 0.9 and 0.8 (other methyl protons).

MS : m/z 489 (M^+), 471 ($M^+ - H_2O$).

Further elution with light petroleum-ethyl acetate (3:1) and recrystallization from light petroleum afforded 3β-acetoxy-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXVI) (305 mg), m.p. 256-258°.

Analysis Found : C, 71.21, H, 10.12, N, 5.32

$C_{30}H_{52}N_2O_4$ requires : C, 71.42, H, 10.31, N, 5.55%.

IR : $\nu_{max.}$ 3450 (-NH and -OH), 1730 (-OCOCH$_3$), 1680 and 1520 (-NH-CO-NH_2), 1270 and 1050 cm^{-1} (C-O).

^{1}H-NMR : δ 5.15 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H), 4.73 (d, J = 7 Hz, -NH_2), 4.2 (m, -NH-), 4.1 (m, C6α-H), 2.4 (br s, -OH, disappears on addition of D_2O), 2.0 (s, -OCOCH_3), 1.1 (C10β-CH_3), 0.65 (C13β-CH_3), 0.86 and 0.80 (other methyl protons).

MS : m/z 504 (M^+), 486 ($M^+ - H_2O$), 442 (M^+ - AcOH).

Elution with light petroleum-ethyl acetate (1:1) gave 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (CXXXVII) (134 mg),

m.p. 208° (reported[34] m.p. 209°).

Further elution with light petroleum-ethyl acetate (1:5) afforded 3β-acetoxy-5-hydroxy-6β-amino-N-carboxy-5α-cholestane (CXXXVIII) (127 mg) as non-crystallizable oil.

Analysis Found : C, 75.42, H, 11.04, N, 2.03

$C_{29}H_{51}NO_3$ requires : C, 75.48, H, 11.06, N, 3.03%.

IR : $\nu_{max.}$ 3480 (-NH, -OH), 1730 (-O-$\underset{\underset{O}{\|}}{C}$-$CH_3$), 1720 (-COOH), 1280 and 1030 cm^{-1} (C-O).

^{1}H-NMR : δ 9.35 (br s,-COOH), 5.2 (m, -NH-), 4.85 (m, $W\frac{1}{2}$ =18 Hz, C3α-H), 4.2 (m, C6α-H), 3.0 (br s, -OH, dissappeared on D_2O addition), 2.0 (s, -OCOCH_3), 1.0 (C10β-CH_3), 0.65 (C13β-CH_3), 0.85 and 0.77 (other methyl protons).

MS : m/z 461 (M^+).

Acetylation of 3β-acetoxy-5-hydroxy-6β-amino-N-amido-5α-cholestane (CXXXVI)

The compound (CXXXVI) (100 mg) was dissolved in acetic anhydride (10 ml) and pyridine (15 ml) and heated over water bath for one hr. The reaction mixture was poured in cold water and taken up in ether. It was washed with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Ether was evaporated and the residue was recrystallized from light petroleum to give 3β,5-diacetoxy-6β-amino-N-amido-5α-cholestane (CXXXIX) (80 mg), m.p. 201-204°.

Analysis Found : C, 70.34, H, 9.86, N, 5.10

$C_{32}H_{54}N_2O_5$ requires : C, 70,32, H, 9.89, N, 5.12%.

IR : $\nu_{max.}$ 3510 (-NH, -OH), 1680 and 1520 ($-NH-CO-NH_2$), 1730 ($-O-\underset{\underset{O}{\|}}{C}-CH_3$), 1290 and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 5.15 (m, $W\frac{1}{2}$ = 18 Hz, C3α-H), 4.55 (d, J = 8 Hz, $-NH_2$), 4.1 (m, -NH-, C6α-H), 2.1 (s, $-COOCH_3$), 2.0 (s, $-OCOCH_3$), 1.1 (C10β-CH_3), 0.63 (C13β-CH_3), 0.86 and 0.78 (other methyl protons).

MS : m/z 546 (M^+).

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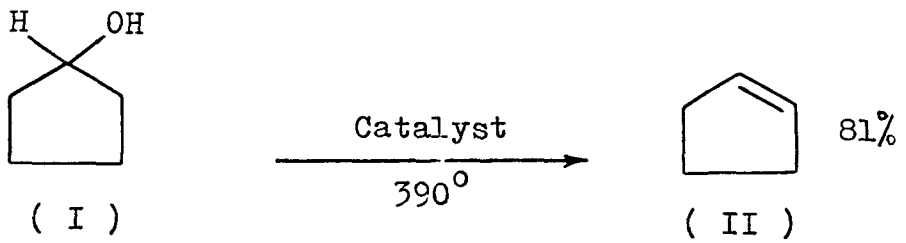
Part-Five

Steroidal Transformations on Solid Surface

THEORETICAL

Postner[1] has reviewed organic reactions on alumina surface. Pines[2] has proposed that alumina prepared by hydrolysis of aluminium isopropoxide is relatively strongly acidic and causes extensive isomerization of the olefins initially formed from the dehydration of alcohols. The isomerization can be suppressed by exposing the catalyst to bases. Dehydration takes place preferentially from adjacent trans (diaxial) hydrogen and hydroxyl group.

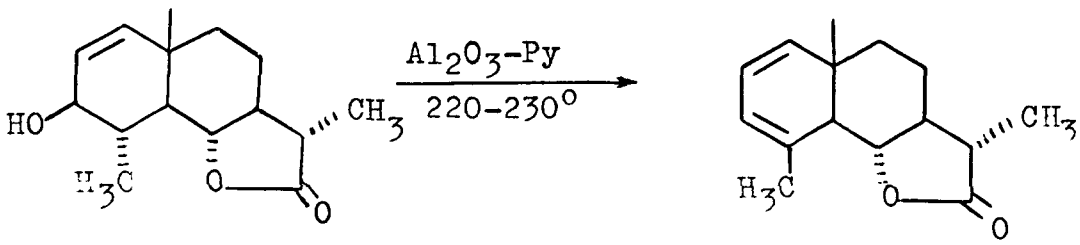
Stoll et al.[3] prepared a dehydration catalyst by moistening a mixture of alumina, diatomaceous earth, cook powder and heating with cyclopentanol (I) to get cyclopentene (II).



(I) (II)

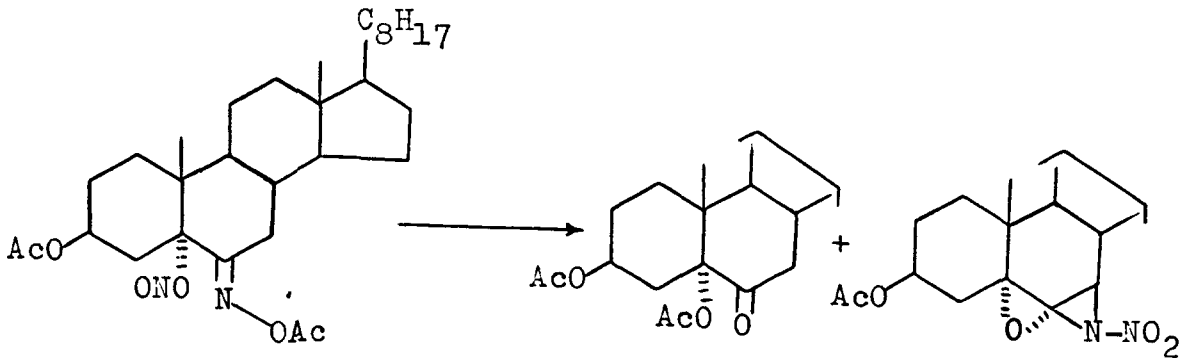
Rudolf[4] found that dehydration of terpene and sesquiterpene alcohols is advantageously carried out with natural alumina. Corey and Hartmann[5] applied this procedure

to the allylic alcohol lactone (III) from Santonin and obtained the diene lactone (IV) in 44% yield.



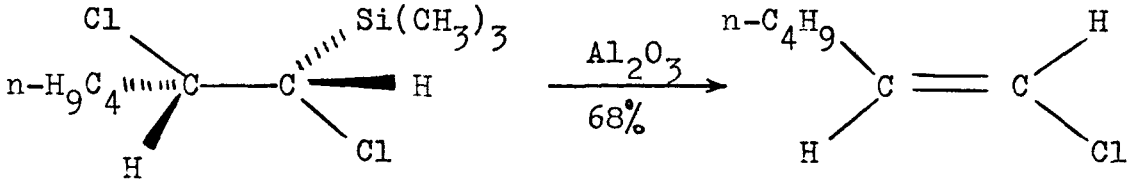
(III) (IV)

An alumina induced reaction of 6-acetoximino-3β-acetoxycholest-5α-ol nitrite (V) gave VI and VII[5].



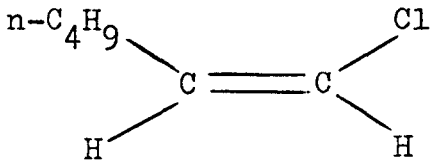
(V) (VI) (VII)

Miller and T. Reichenbach[6] prepared vinyl halides from vinyl silane by hydrogenation followed by elimination of $ClSi(CH_3)_3$ with sodium methoxide or neutral alumina. The stereoselectivity was high with trans-vinylsilanes but somewhat lower with cis-vinylsilanes.



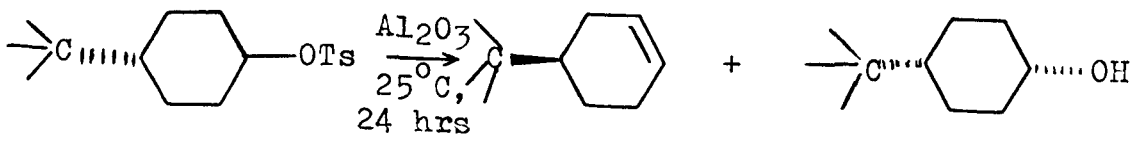
(VIII) (IX)

+

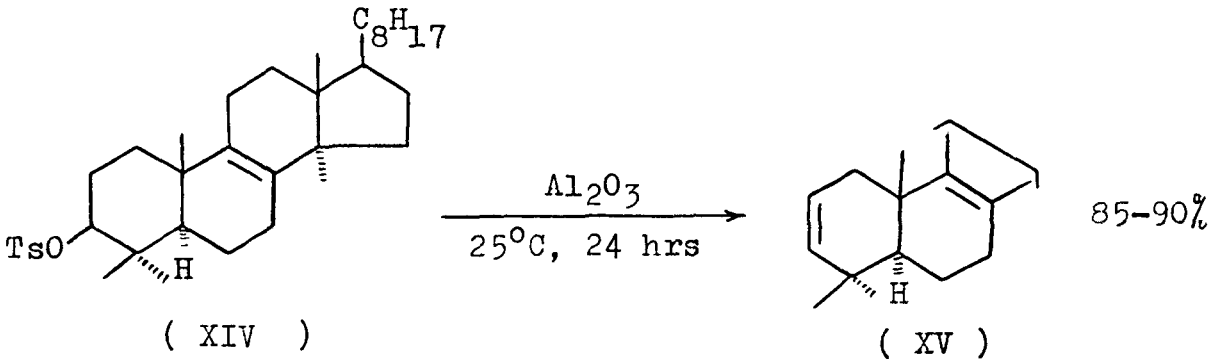


(X)

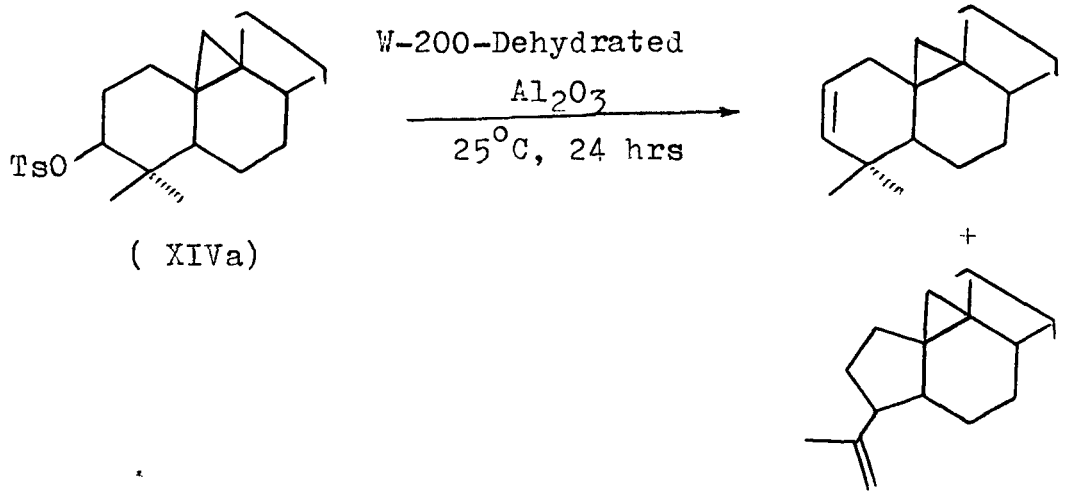
Posner[7] et al. converted some sulphonate esters into alkenes conveniently by treatment with ω-200-N alumina[7].



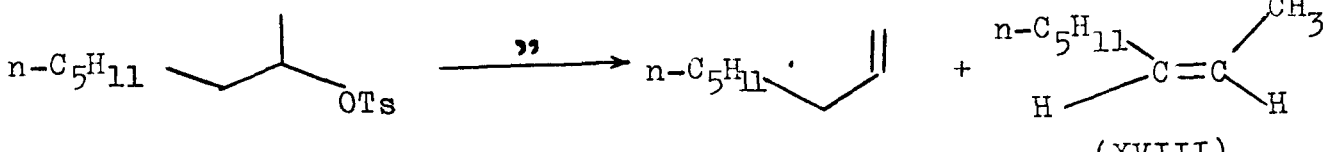
(XI) (XII) (XIII)



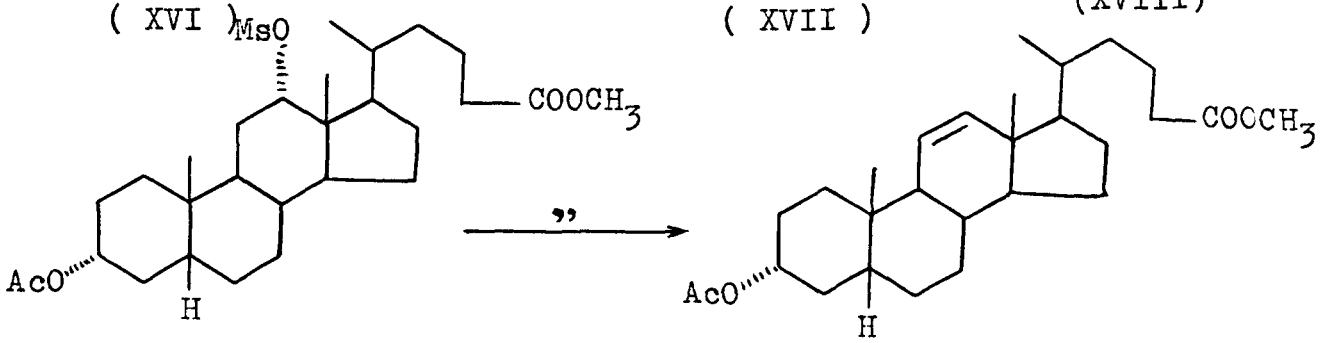
(XIV) (XV)



(XIVa) (XVa)

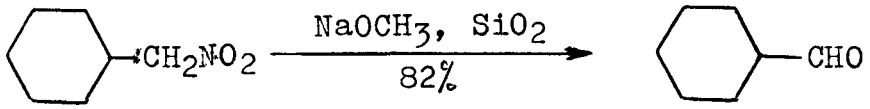


(XVI) (XVII) (XVIII)

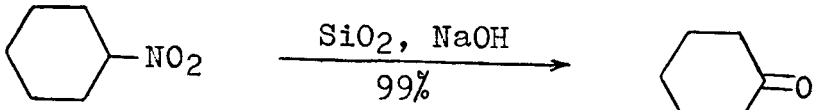


(XIX) (XX)

Keinan and Mazur[8] devised a useful and mild version of Nef reaction[9] which utilized basic silica gel. It was used for converting 1-nitromethylcyclohexane (XXI) to 1-cyclohexane carboxaldehyde (XXII) by Hogg et al.[10].



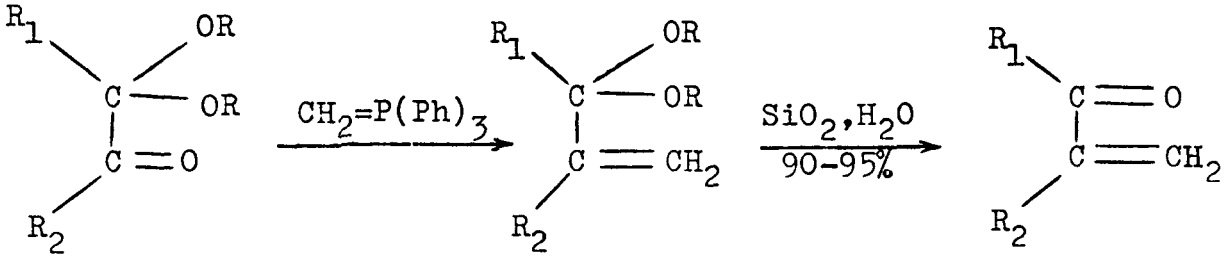
(XXI) (XXII)



(XXIII) (XXIV)

$$CH_3(CH_2)_5\text{-}CH_2NO_2 \xrightarrow[87/]{NaOCH_3, SiO_2} CH_3(CH_2)_5CHO$$

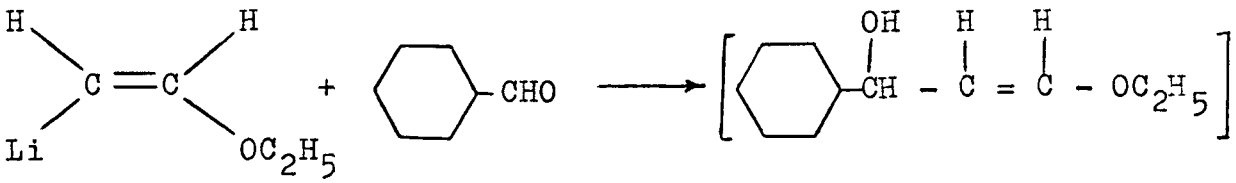
Alkyl ketones were prepared in high yields by reaction of α-haloketals with Wittig reagent and a base followed by deketalization with wet silica gel[11].



R = alkyl (XXVI) (XXVII)

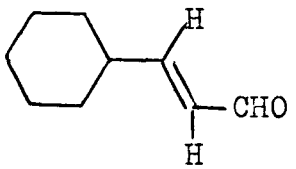
(XXV)

Two groups[12,13] have simultaneously reported the preparation of cis-1-ethoxyvinyllithium (XXVIII) and its reaction with aldehyde and ketone to form enol ester (XXIX), which was readily converted into α,β-unsaturated aldehyde (XXX) by acetic acid or chromatography over silica gel or Floricil.



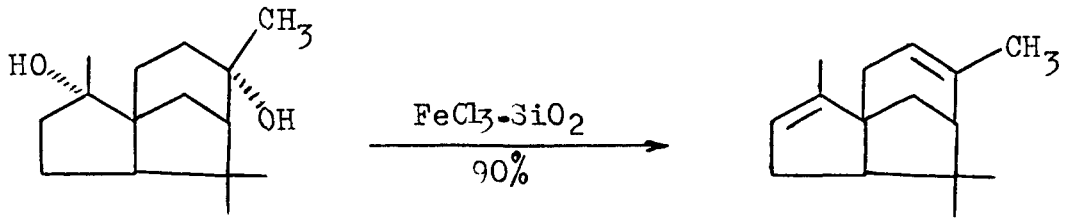
(XXVIII) (XXIX)

89%

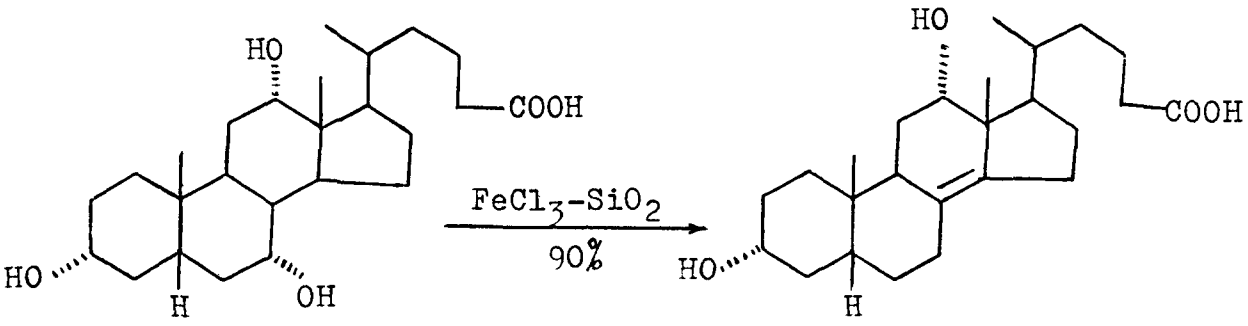


(XXX)

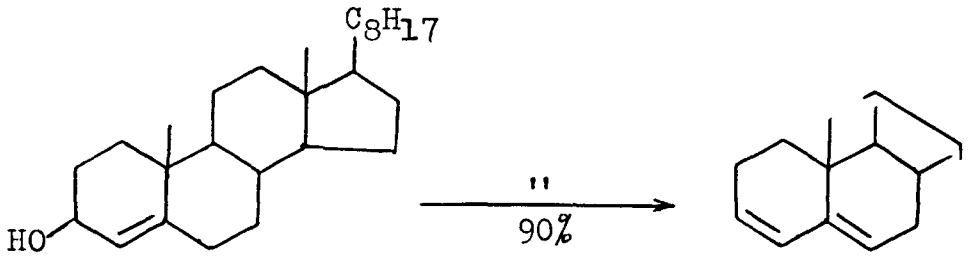
Keinan and Mazur[14] used $FeCl_3$ solution mainly as mild oxidantwhen absorbed over silica gel.



(XXI) (XXXII)

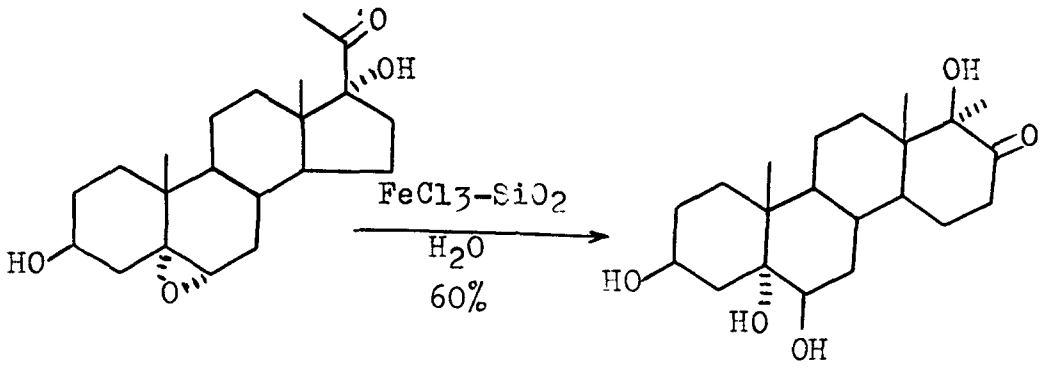


(XXXIII) (XXXIV)

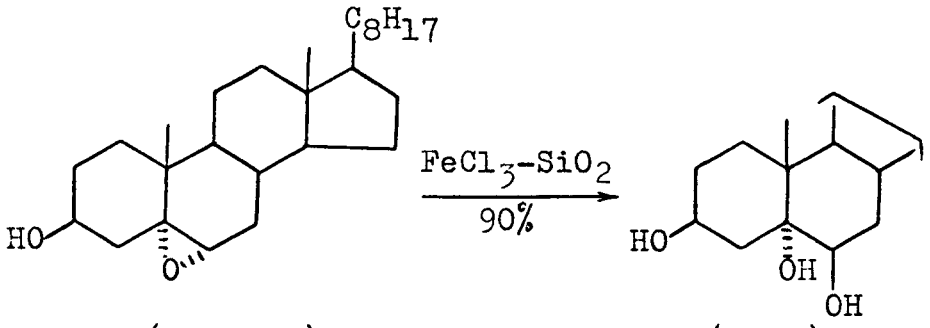


(XXXV) (XXXVI)

The same reagent, when wet, converted epoxide (XXXVII, XXXIX) into triol[14] (XXXVIII, XL).

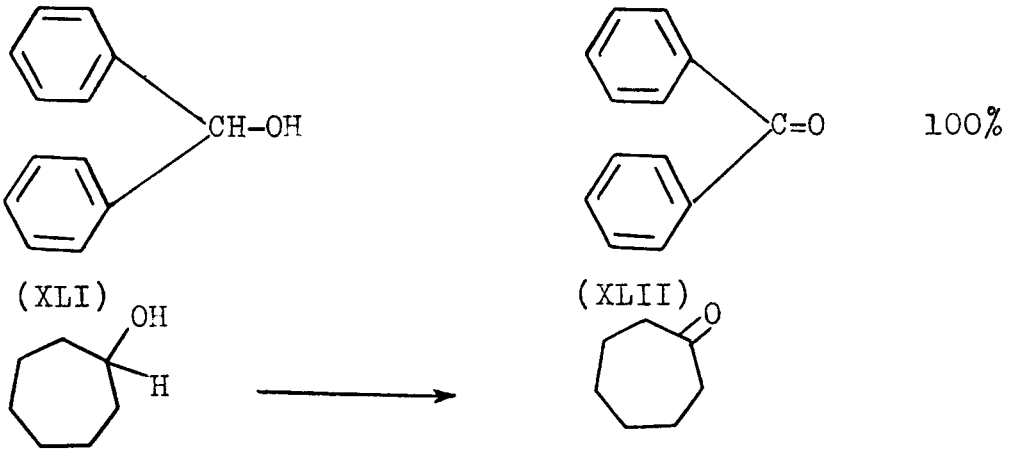


(XXXVII) (XXXVIII)



(XXXIX) (XL)

Regen and Koteel[15] oxidized secondary alcohols into ketones by the impregnation of oxidants like potassium permangnate on an inorganic solid support such as molecular sieve, silica gel and certain clays.

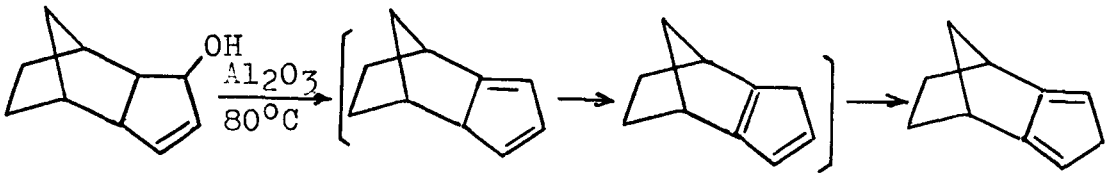


(XLI) (XLII)

(XLIII) (XLIV)

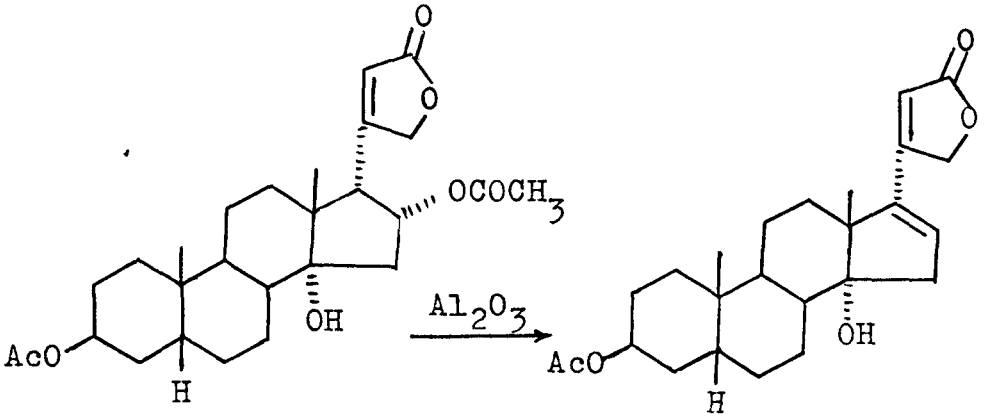
Chromic acid adsorbed on silica gel was found to be useful for oxidation of primary and secondary alcohols to carbonyl compounds in 80-90% yield. In contrast, H_2CrO_4 adsorbed on alumina was ineffective[16].

Paquette et al.[17] carried out the dehydration of tricyclic alcohol (XLV) over alumina at 180°C which yielded a hydrocarbon known as isodicyclopentadiene (XLVI)[18,19].



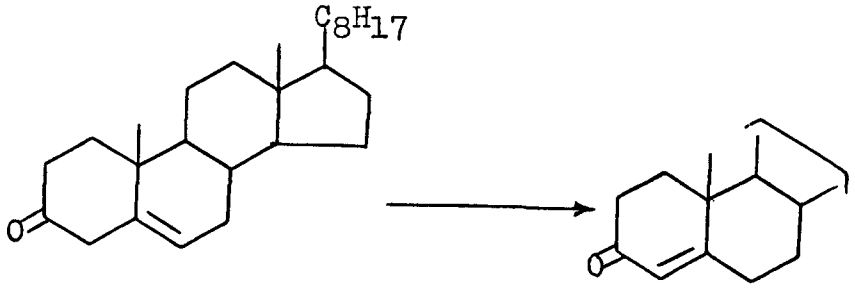
(XLV) (XLVI)

Many interesting reactions produced by alumina have been reported in the steroid field such as saponification of steroid benzoates[20], the splitting out of a molecule of acetic acid from a sterol acetate with the formation of a double bond[21].



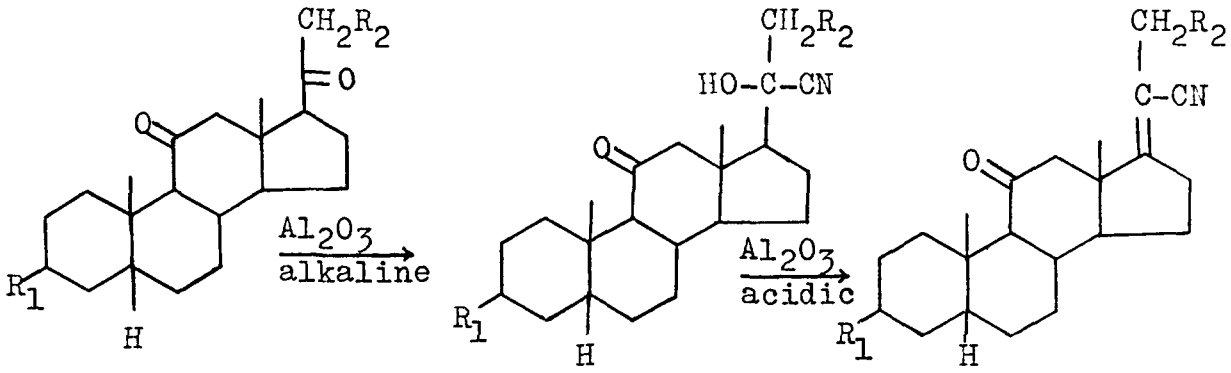
(XLVII) (XLVIII)

Reichstein and Shoppee[22] reported that Δ^5-3-ketone (XLIX) undergoes isomerization to Δ^4-3-ketone (L) by alumina containing alkali, but not when neutralized Al_2O_3 is employed[23].



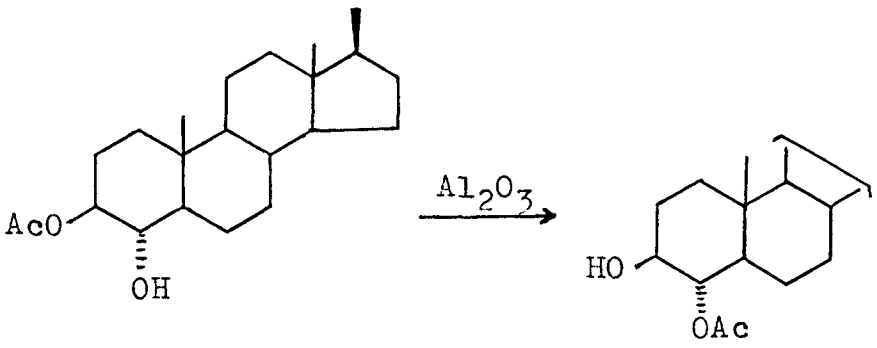
(XLIX) (L)

Fieser[24] observed a similar migration of double bond with acid washed alumina. Elks et al.[25] found that the conversion of Δ^9-7-keto steroid to Δ^8-7-keto steroid can be avoided by treatment of the alumina with acetic acid and reactivation by heating. Sarett[26] observed two interesting reactions of steroid cyanohydrin (LI); when passed through an acid washed alumina column, the steroid was dehydrated to give an unsaturated nitrile (LII) whereas a column of alkaline alumina caused the elimination of a molecule of HCN to regenerate the original ketone (LIII) in 90% yield.



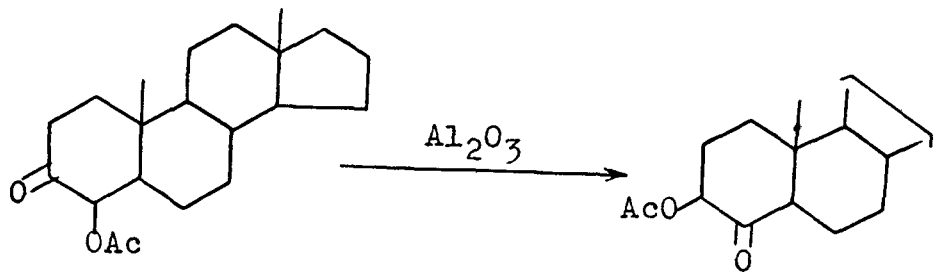
(LIII) (LI) (LII)

Lieberman and Fukushima[27] reported acyl migration of monoacetate of 3,4-diol on alumina.



(LIV) (LV)

Fieser and Stevenson[28] described the isomerization of a 3-keto-4-acetate (LVI) to a 3-acyl-4-keto steroid (LVII).



(LVI) (LVII)

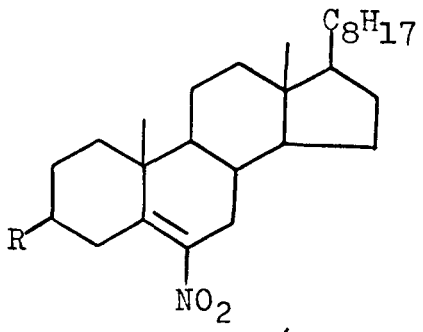
DISCUSSION

Alumina as catalyst or as catalyst support finds multiple uses in general important industrial processes like dehydration, isomerization, craking polymerization, condensation and alkylation[29]. Alumina samples obtained from different sources are found to posses different activities[30]. The presence of acid sites over alumina have been acknowledged through the nature of acidity, whether Bronsted or Lewis type, has been a point of controversy[31,32]. Further reactivity and selectivity of the catalytic alumina change with the impregnation of the alkali or halide ions[29,33]. The presence of Lewis acid sites over alumina surfaces and also its importance in bringing about reactions such as different types of isomerization of olefins[34] are well recognized[35]. In some cases the commercial material can be used directly. Dehydrated alumina at 400°C under vacuum is sometimes more efficient. The dehydrosulphonation of alumina is particularly useful for some secondary sulphonate esters when elimination in one direction is favoured by stereoelectronic factor or by absence of β-hydrogen atom. The method is generally less useful for primary systems[7]. Similarly silica gel is an effective reagent for rapid dehydration of

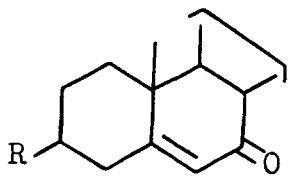
allylic, tertiary and sterically hindered secondary alcohol at room temperature. Selective dehydration of polyhydroxylic substrates is possible[14].

Conjugated cyclic nitro olefins are potentially versatile and unique as synthetic intermediates, but still the lack of generally suitable and mild processes for the synthesis of cyclic nitro olefins has impeded the development of this whole domain of synthetic methodology[36].

In view of the useful catalytic behaviour exhibited by alumina and silica gel in bringing about some of the selective chemical transformations we have carried out the solid surface reaction of some of the steroidal nitro compounds such as 3β-hydroxy-6-nitrocholest-5-ene (LVIII), its 3β-acetoxy (LIX) and 3β-chloro (LX) analogues and some steroidal α,β-unsaturated ketones such as 3β-hydroxycholest-5-en-7-one (LXI) and 3β-acetoxycholest-5-en-7-one (LXII). We have thus, developed a very mild, convenient, and high yielding method for converting nitro olefins into nitro dienes and α,β-unsaturated ketones to dienones.



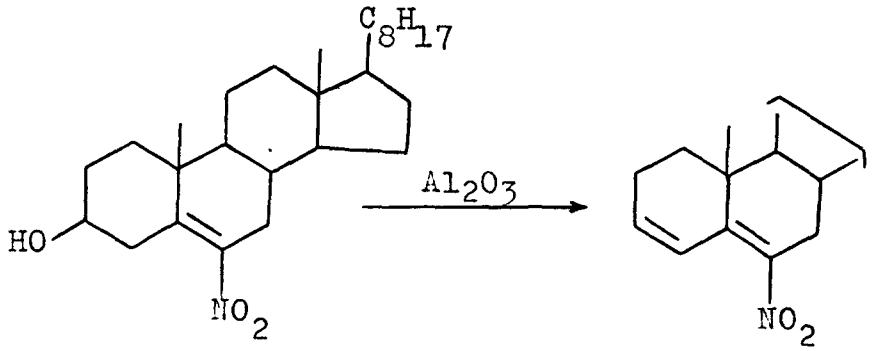
	R
(LVIII)	OH
(LIX)	OAc
(LX)	Cl



	R
(LXI)	OH
(LXII)	OAc

Reaction of 3β-hydroxy-6-nitrocholest-5-ene (LVIII) with basic alumina

The compound (LVIII) dissolved in dry ether, was adsorbed over preheated (200°C) and cooled basic aluminium oxide (chromatographic analysis grade). The residual solvent was removed under reduced pressure and the reaction mixture was kept at room temperature for 48 hrs. Elution with ether provided compound (LXII) m.p. 72°.



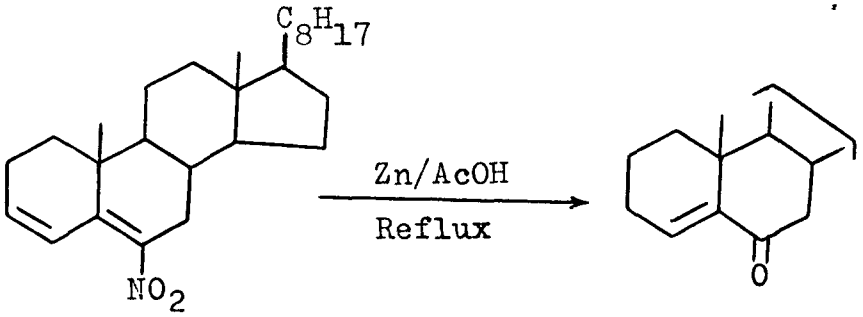
(LVIII) (LXIII)

Characterization of compound, m.p. 72° as 6-nitrocholesta-3,5-diene (LXIII)

The compound (LXIII) m.p. 72° was analysed for $C_{27}H_{43}NO_2$ and gave a molecular ion peak at m/z 413, The IR spectrum displayed a band at 1680 cm^{-1} for (C=C-C=C-NO_2) and other band of similar medium intensity was observed at

1630 cm^{-1} for carbon carbon double bond. Strong bands at 1515 and 1350 cm^{-1} suggested the presence of nitrogroup in the molecule. The NMR spectrum exhibited a doublet (J = 10 Hz) for C4 proton at δ 6.5 and a multiplet ascribed for C3 proton at δ 6.0. Methyl signals appeared at δ 1.05 (C10β-CH_3), 0.7 (C13β-CH_3), 0.9 and 0.8 (other methyl protons). The above data were in full support for the proposed structure of 6-nitrocholesta-3,5-diene (LXIII).

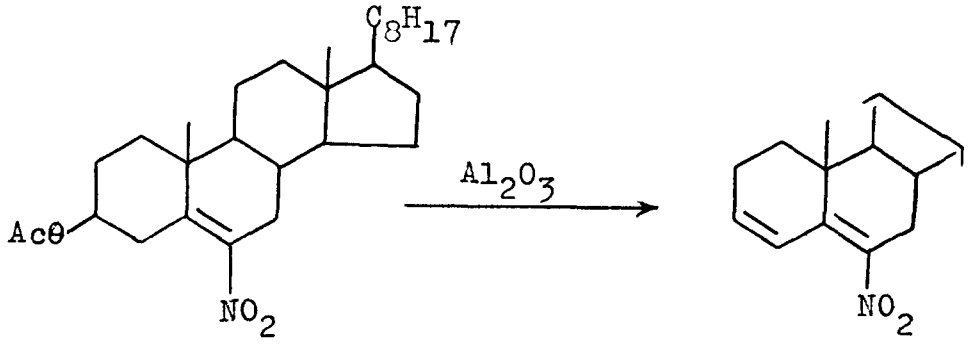
The chemical evidence for the compound (LXIII) was obtained by its conversion through reductive hydrolysis with zinc and acetic acid to the known cholest-4-en-6-one (LXIV) m.p. 107-108° (reported[37] m.p. 108-109°).



(LXIII) (LXIV)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LIX) with basic alumina

3β-Acetoxy-6-nitrocholest-5-ene (LIX) was treated with basic alumina as described earlier and product m.p. 72° was eluted with ether.



(LIX) (LXIII)

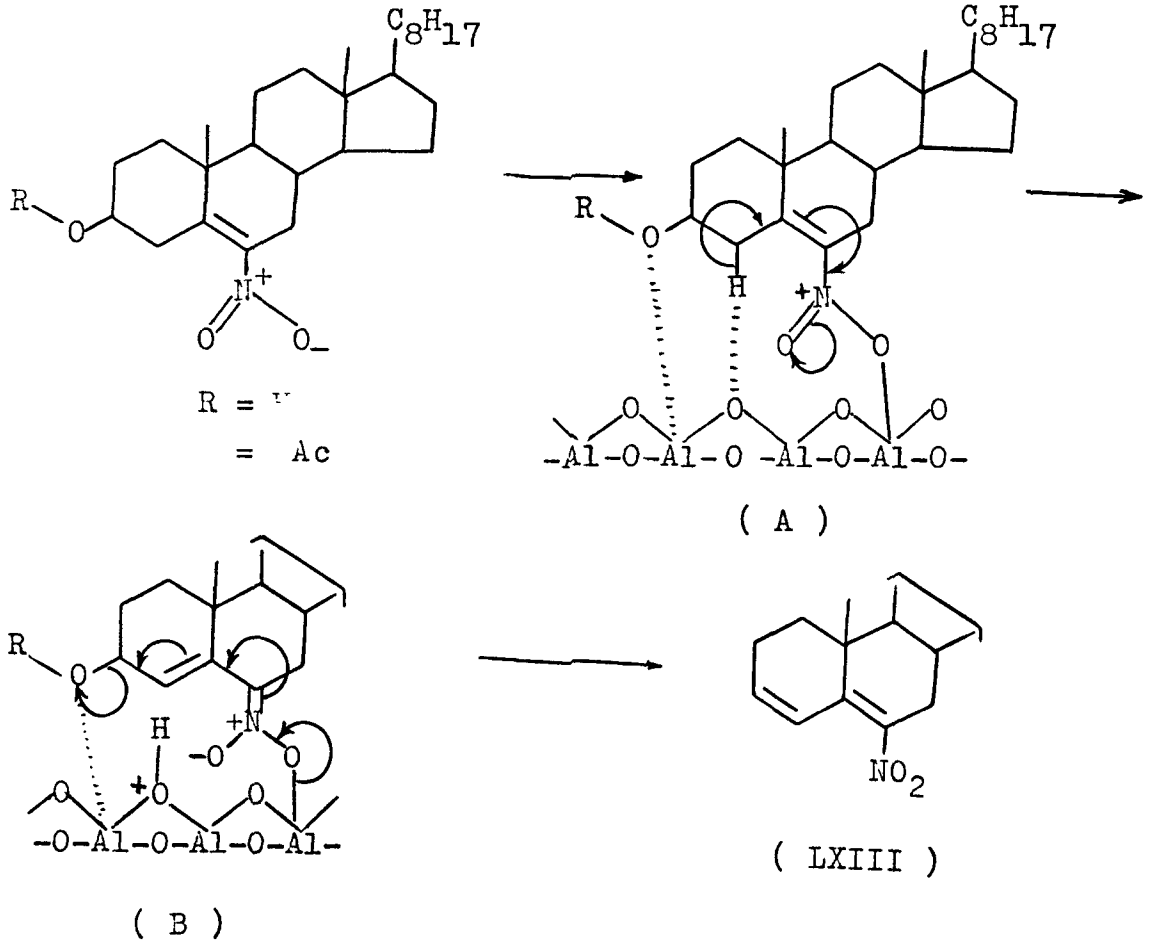
Characterization of the compound m.p. 72° as 6-nitrocholesta-3,5-diene (LXIII)

The compound (LXIII), m.p. 72° was characterized as 6-nitrocholesta-3,5-diene on the basis of its spectral properties. The compound was found to be identical in all respects (TLC, m.p., m.m.p.) with 6-nitrocholesta-3,5-diene obtained from 3β-hydroxy-6-nitrocholest-5-ene (LVIII).

Reaction of 3β-chloro-6-nitrocholest-5-ene (LX) with basic alumina

On similar treatment, 3β-chloro-6-nitrocholest-5-ene (LX) under similar reaction conditions failed to react with basic alumina and elution with ether yielded only the starting material.

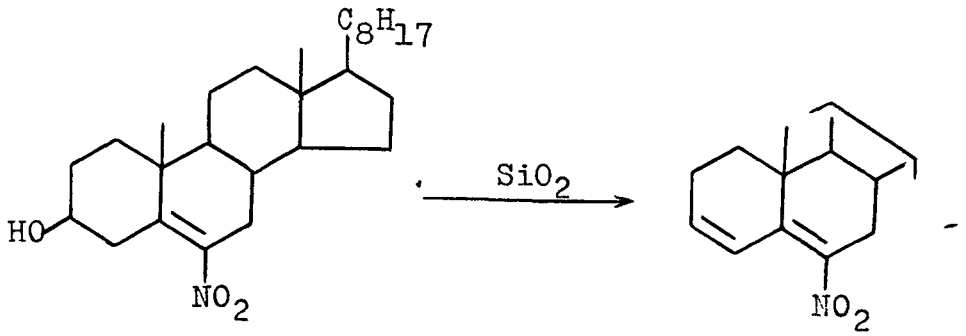
The mechanism for the above transformation was suggested as follows:-



The above mechanism was able to explain the non-reactivity of 3β-chloro-6-nitrocholest-5-ene (LX) with basic alumina under similar reaction conditions. The participation of oxygen atom was explained through the reaction intermediates (A) and (B) finally leading to the product.

Reaction of 3β-hydroxy-6-nitrocholest-5-ene (LVIII) with basic silica gel[38]

3β-Hydroxy-6-nitrocholest-5-ene (LVIII) was dissolved in dry ether and to this was added basic silica gel. The ether was removed under reduced pressure and the residual mass was kept at room temperature for 48 hrs. The yellow silica gel was eluted with ether, to afford a compound m.p. 72°.



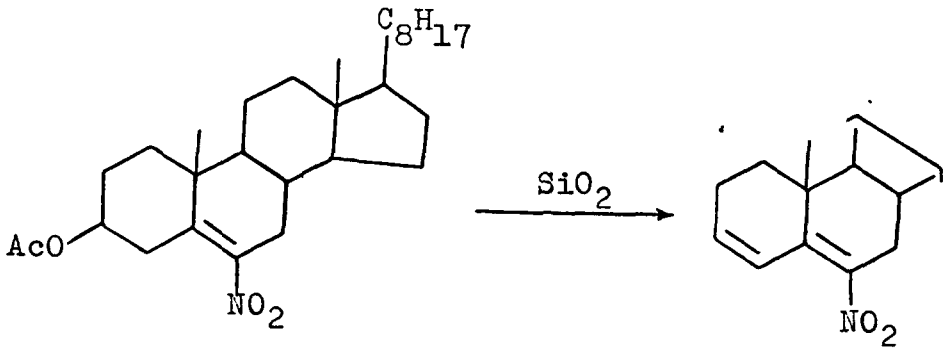
(LVIII) (LXIII)

Characterization of the compound m.p. 72° as 6-nitrocholesta-3,5-diene (LXIII)

The compound (LXIII) m.p. 72° was characterized on the basis of its spectral and chemical properties and on comparison with authentic sample (TLC, m.p., m.m.p.) of 6-nitrocholesta-3,5-diene (LXIII).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LIX) with basic silica gel[38]

A solution of 3β-acetoxy-6-nitrocholest-5-ene (LIX) in dry ether was added to basic silica gel. The solution was mixed and the solvent was evaporated under reduced pressure and kept at room temperature for 48 hrs. The compound (LXIII), m.p. 72° was eluted with ether.



(LIX) (LXIII)

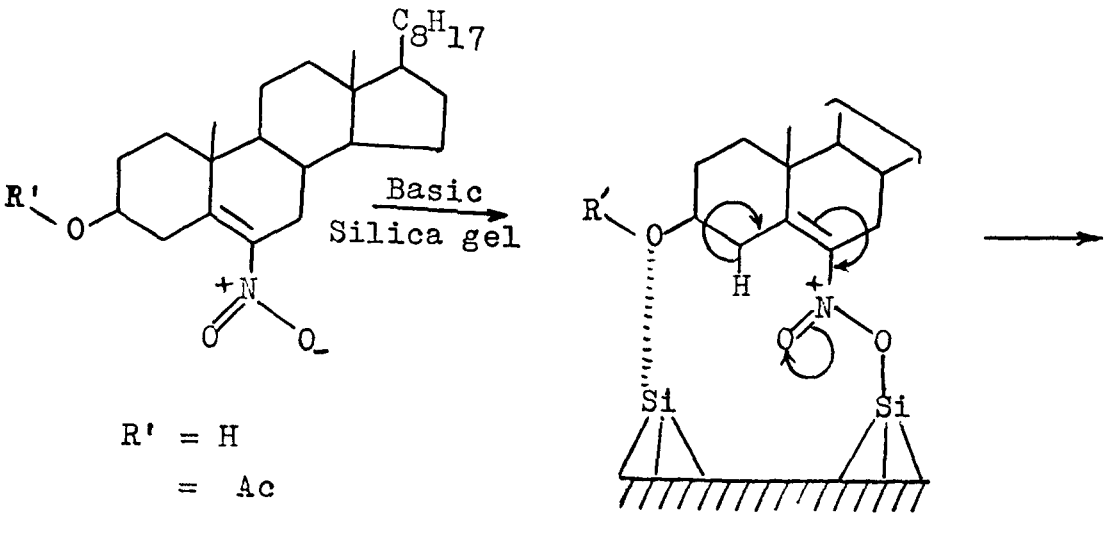
Characterization of the compound (LXIII) m.p. 72° as 6-nitrocholesta-3,5-diene

The compound (LXIII), m.p. 72° was characterized on comparison (TLC, m.p., m.m.p. IR and NMR) with authentic sample of 6-nitrocholesta-3,5-diene (LXIII) obtained from previous reactions.

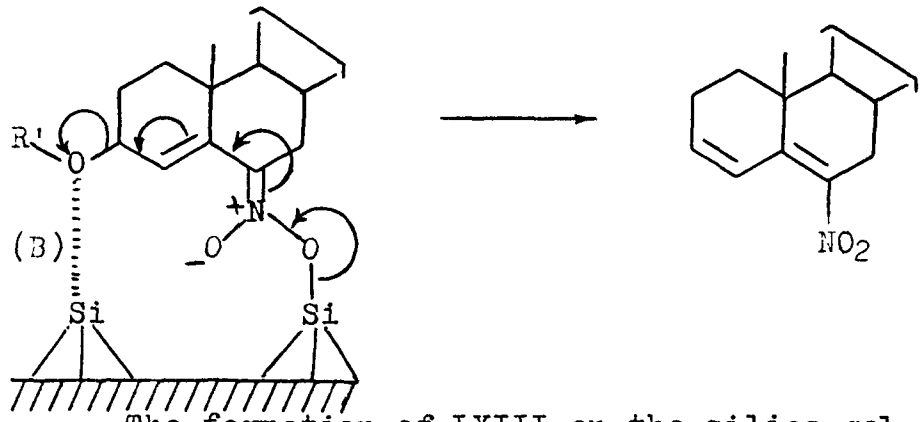
Reaction of 3β-chloro-6-nitrocholest-5-ene (LX) with basic silica gel

3β-Chloro-6-nitrocholest-5-ene (LX) on similar treatment with basic silica gel did not react at all even on prolonged period at room temperature.

The mechanism of the proposed reaction was given as follows:



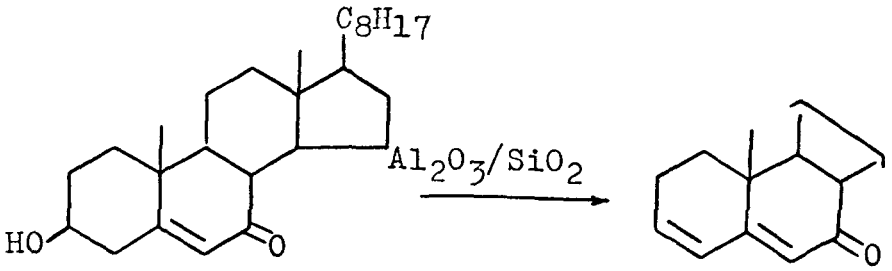
(A)



The formation of LXIII on the silica gel surface probably occurs through the intermediacy of (A) and (B). This finds support from the fact than 3β-chloro-6-nitrocholest-5-ene (LX) under similar reaction conditions failed to react. This observation supported the participation of oxygen atom at C3 in the reaction intermediate (A) leading to (B) containing a nitronate ion[38] and finally to product LXIII. The reaction provided a simple method for dehydration of alcohol to conjugated diene system attached to nitro group. The same compound (LXIII) was prepared by one of us through other synthetic route[38a].

Reaction of 3β-hydroxycholest-5-en-7-one (LXI) with basic alumina/silica gel[38]

3β-Hydroxycholest-5-en-7-one (LXI) (500 mg) was dissolved in dry ether and adsorbed over basic alumina/silica gel (10 g). The ether was removed under reduced pressure and the residual mass was kept a room temperature for 48 hrs. Silica gel was eluted with ether to give a compound m.p.116°.



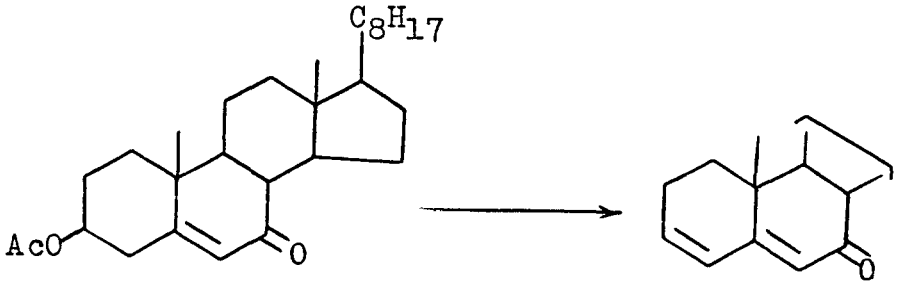
(LXI) (LXV)

Characterization of the compound m.p. 116° as cholesta-3,5-dien-7-one (LXV)

The compound (LXV) m.p. 116° was analysed correctly for $C_{27}H_{42}O$. The IR spectrum of the compound showed weak intensity band at 3020 cm^{-1} for vinylic proton stretching frequency and a strong band at 1670 cm^{-1} for α-unsaturated carbonyl group absorption. Another band at 1620 cm^{-1} was ascribed for carbon carbon double bond. The NMR spectrum displayed a singlet for two protons at δ 6.08 assigned to C3 and C4 protons. Another singlet for one proton appeared at δ 5.5 was due to C6 vinylic proton . Methyl signals were seen at δ 1.15 (C10β-CH_3), 0.71 (C13β-CH_3), 0.95 and 0.85 (other methyl protons). On the basis of forgoing discussion and its comparison with authentic sample, the compound (LXV)was identified as cholesta-3,5-dien-7-one (reported[39] m.p. 118°).

Reaction of 3β-acetoxycholest-5-en-7-one (LXII) with basic alumina/silica gel[38]

Similar treatment of 3β-acetoxycholest-5-en-7-one (LXII) (500 mg) with basic alumina/silica gel (10 g) provided a compound m.p. 116°.



(LXII) (LXV)

Characterization of compound m.p. 116° as cholesta-3,5-dien-7-one (LXV)

The compound (LXV) was characterized on the basis of its spectral propeties and comparison with authentic sample[39] (TLC, m.p., m.m.p.) as cholesta-3,5-dien-7-one (LXV).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer 237 and Unichem SP300 spectrophotometers. The NMR spectra were run in $CDCl_3$ on Varian A60 instrument with TMS as internal standard. Mass spectra were run on JEOL JMS D300 mass spectrophotometer at 70 eV at the source temperature of 120°C. Thin layer chromatographic plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Silica gel, chromatographic grade was used to prepare basic silica gel. Basic alumina chromatographic grade, BDH, was used after drying at 200°C. Light petroleum refers to a fraction of b.p. 60-80°. NMR values were given in ppm (s, singlet; d, doublet; t, triplet; br, broad; mc, multiplet centred at). IR values are given in cm^{-1} (s, strong; m, medium; w, weak, br, broad).

Preparation of basic silica gel

Basic silica gel was prepared by mixing chromatographic grade silica gel (60-120 mesh) with a solution of NaOH in methanol followed by evaporation to dryness and heating at 400° for several hrs. The resulting dry powder (containing 0.5 equiv. of sodium per Kg of silica gel) can be stored in bottles. Silica gel containing higher concentrations of

sodium ions can also be used[38].

3β-Hydroxy-6-nitrocholest-5-ene (LVIII)

3β-Acetoxy-6-nitrocholest-5-ene (1 g) was dissolved in methanol (80 ml) and KOH (1 g) was added to it. The mixture was refluxed on water bath for 2 hrs. The reaction mixture was poured in cold water, acidified with dil. HCl and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the ether gave an oil which was crystallized from methanol to give (LVIII), m.p. 128-129° (reported[40] m.p. 129-131°).

3β-Acetoxycholest-5-en-7-one (LXII)

A solution of t-butyl chromate (t-butyl alcohol 60 ml; CrO_3, 20 g; acetic acid 84 ml and acetic anhydride 10 ml) was added at 0°C to a solution of 3β-acetoxycholest-5-ene (8 g) in carbon tetrachloride (150 ml), acetic acid (30 ml) and acetic anhydride (10 ml). The contents were refluxed for 3 hrs and then it was diluted with water. The organic layer was washed successively with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure furnished an oil which was crystallized in methanol to give the ketone (LXII) (4 g), m.p. 162° (reported[41] m.p. 164°).

3β-Hydroxycholest-5-en-7-one (LXI)

3β-Acetoxycholest-5-en-7-one (1 g) was taken in methyl alcohol (500 ml) and a solution of potassium carbonate(K_2CO_3 3 g in 30 ml of water) was added. The mixture was shaken mechanically at 20°C for 20 hrs. The clear yellow liquid was diluted with water concentrated under reduced pressure at 20°C to small bulk, extracted with ether, washed with water and dried (Na_2SO_4). The solvent was removed by distillation. The residue was crystallized from hot methyl alcohol by addition of water untill almost cloudy (350 mg), m.p. 159-161°. Recrystallizarion from ether-light petroleum provides needle shaped crystals of the compound (LXI) m.p. 160°.

Reaction of 3β-hydroxy-6-nitrocholest-5-ene (LVIII) with basic alumina/silica gel: 6-Nitrocholesta-3,5-diene (LXIII)

A solution of 3β-hydroxy-6-nitrocholest-5-ene (LVIII) (500 mg) in dry ether (10 ml) was adsorbed over basic alumina (heated at 200°, cooled and desiccated) or basic silica gel (10 g). The residual ether was removed under reduced pressure and the reaction mixture was kept at room temperature for 48 hrs. The compound was eluted from alumina/silica gel with ether. The solvent evaporation yielded a semisolid which was crystallized from methanol as yellow shining crystals (450 mg), m.p. 72° (reported[42] m.p. 72-73°).

Analysis Found : C, 78.40, H, 10.39, N, 3.39

$C_{27}H_{43}NO_2$ requires : C, 78.45, H, 10.41, N, 3.38%.

IR : $\nu_{max.}$ 1680 ($-C=C-C=C-NO_2$), 1630 ($-C=C-$), 1515 and 1350 ($-C-NO_2$), 1100, 970, 930, 815 and 780 cm^{-1}.

^{1}H-NMR : δ 6.5 (d, C4-H, J = 16 Hz), 6.0 (m, C3-H), 1.05 (C10β-CH_3), 0.7 (C13β-CH_3), 0.9 and 0.8 (other methyl protons).

Reaction of 3β-acetoxy-6-nitrocholest-5-ne (LIX) with basic alumina/silica gel: 6-Nitrocholesta-3,5-diene (LXIII)

The compound (LIX) (500 mg) dissolved in dry ether (10 ml), adsorbed over basic alumina/silica gel, was kept at room temperature for 48 hrs. The mixture was eluted with ether and product (LXIII) was crystallized from methanol (445 mg) as yellow shining crystals, m.p. 72° (reported[40] m.p. 72-73°).

Reductive hydrolysis of 6-nitrocholesta-3,5-diene (LXIII) with zinc and acetic acid: Cholest-4-en-6-one (LXIV)

6-Nitrocholesta-3,5-diene (LXIII) (200 mg) was dissolved in glacial acetic acid (10 ml) and to this zinc powder (500 mg) was added gradually with shaking. After the initial exothermic reaction had subsided, the suspension was heated under reflux for 3 hrs and 3 ml water was added during this period. The solution was filtered and the residue was washed with warm

acetic acid (5 ml). Ice cooled water was added to the filtrate and the compound was taken up in ether, washed with water, $NaHCO_3$ solution (5%) and water, and dried over anhydrous sodium sulphate. The solvent evaporation provided a semisolid which was crystallized from ethanol (120 mg), m.p. 108° (reported[37] m.p. 108-109°).

Reaction of 3β-hydroxycholest-5-en-7-one (LXI) with basic alumina/silica gel: Cholesta-3,5-dien-7-one (LXV)

A solution of 3β-hydroxycholest-5-en-7-one (LXI) (500 mg) in dry ether (10 ml) was adsorbed over basic alumina/silica gel (10 g). The residual ether was removed under reduced pressure and the reaction mixture was kept at room temperature for 48 hrs. The compound was eluted from alumina/silica gel with ether. The solvent evaporation yielded a semisolid which was crystallized from methanol as shining crystals, m.p. 116° (rported[39] m.p. 118°).

Analysis Found : C, 84.76; H, 10.81

$C_{27}H_{42}O$ requires : C, 84.81; H, 10.99%.

IR : $\nu_{max.}$ 3020 (-C=C(H)-), 1670 (C=C-C=O), 1620 (-C=C-)

^{1}H-NMR : δ 6.08 (m, C3-H and C4-H), 5.5 (s, C6-H), 1.15 (C10β-CH_3), 0.71 (C13β-CH_3), 0.95 and 0.85 (other methyl protons).

Reaction of 3β-acetoxycholest-5-en-7-one (LXII) with basic alumina/silica gel: Cholesta-3,5-dien-7-one (LXV)

A solution of 3β-acetoxycholest-5-en-7-one (LXII) (500 mg) in dry ether was adsorbed over basic alumina/silica gel and residual ether was removed. The reaction mixture was kept at room temperature for 48 hrs and product was eluted with ether which on evaporation gave a semisolid which was crystallized from methanol m.p. 116° (reported[39] m.p. 118°).

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